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Childhood-onset epilepsy and long-term child and maternal well-being

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Abstract

The long-term prognosis of pediatric epilepsy is favorable with respect to seizures, whereby 66% to 80% of children attain seizure control. However, psychiatric and psychosocial problems among children with epilepsy (CWE) and their parents are common, and little is known about their long-term outcomes. The objectives of this dissertation were to: 1) validate a parent-reported measure of young adult's health-related quality of life (HRQOL), to allow for a consistent informant to report on CWE's HRQOL from childhood into young adulthood; 2) delineate the long-term course of CWE's HRQOL and identify the clinical, parent, and family characteristics associated with the trajectory of HRQOL; 3) evaluate the long-term HRQOL of mothers of CWE and identify the factors associated with long-term HRQOL; and 4) delineate the long-term course of depressive symptoms for mothers of CWE and identify factors associated with the trajectory of depressive symptoms.

Data came from the Heath-related Quality of Life in Children with Epilepsy Study (HERQULES), a Canada-wide prospective cohort study of 373 children, aged 4 – 12 years, with newly diagnosed epilepsy. Parents completed questionnaires at the time of epilepsy diagnosis, and 0.5, 1, 2, 8, and 10 years later. CWE's and their mothers' HRQOL were measured using the Quality of Life in Childhood Epilepsy Questionnaire, and the Short Form Health Survey, respectively. Mothers' depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale. Latent class growth models were used to evaluate the trajectory of CWE's HRQOL and their mothers' depressive symptoms over the long-term.

We found that changes in CWE's HRQOL observed within the first two years after diagnosis of epilepsy remained stable over the long-term, and that mothers' depressive symptoms largely remained stable over the entire follow-up period . The long-term trajectory of CWE's HRQOL and mothers' depressive symptoms were associated with the severity of epilepsy, neuropsychological comorbidities and family functioning at the time of epilepsy diagnosis. These results are important in identifying long-term outcomes and showing that targeting the family environment early on may lead to optimal HRQOL and mental health for children with epilepsy and their parents.

Keywords: epilepsy, child, mother, quality of life, depression, family environment, trajectory modeling, longitudinal study, long-term outcomes

Summary for Lay Audience

Epilepsy is a condition of the brain characterized by repeated seizures. In the long-term, most children with epilepsy attain seizure control. However, there is increasing evidence about the impact of epilepsy beyond seizures, finding that children and their parents commonly have mental health problems (such as depression) and poor quality of life. Little is known about the long-term outcome of quality of life and mental health for children with epilepsy and their parents. The primary objective of this dissertation was to describe the course of quality of life and depression over the long-term for children with epilepsy and their mothers, respectively. A secondary objective was to identify the characteristics of epilepsy, children, parents, and the family that are associated with the patterns of quality of life and depression observed over time.

Neurologists practising across Canada identified children, aged 4 – 12 years, with newly diagnosed epilepsy. A total of 373 families participated by completing questionnaires at the time of epilepsy diagnosis and 0.5, 1, 2, 8, and 10 years later. At each time parents completed questionnaires reporting on their children's quality of life and their own depressive symptoms.

We found that children's quality of life changed most during the first two years after their epilepsy diagnosis, and remained stable thereafter over the long-term. One-third of children had a relatively poor quality of life at the time of epilepsy diagnosis and throughout the 10-year follow-up. We also found that mothers' depressive symptoms remained stable over the long-term for most mothers, with 20% reporting high scores for depression symptoms throughout the 10-year follow-up. The patterns for children's quality of life and mothers' depressive symptoms over time were poorer among those with a more severe epilepsy, with cognitive/behavioral problems, and poorer family environment at the time of epilepsy diagnosis. These results are important in understanding long-term outcomes and showing that targeting the family environment early on may lead to improvements in quality of life and mental health for children with epilepsy and their parents.

Co-Authorship Statement

For this doctoral dissertation and each of the manuscripts contained within, Klajdi Puka played the primary role of creating the research questions, developing the analysis plan, analyzing the data, and the writing of all components, under the supervisory guidance of Dr. Kathy Nixon Speechley. This dissertation used data obtained from the Health-related Quality of Life in Children with Epilepsy Study (HERQULES) led by Dr. Speechley. The author's supervisor, Dr. Kathy Nixon Speechley, and committee members, Drs. Mark A. Ferro and Kelly K. Anderson provided ongoing contributions in the form of regular feedback and methodological advice throughout the research. Other co-authors contributed to the design of HERQULES and provided feedback once manuscript(s) were drafted. Klajdi Puka was the primary author of each manuscript.

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List of Abbreviations

ASM: antiseizure medications

AYA: Adolescent and young adult

BIC: Bayesian Information Criterion

CES-D: Center for Epidemiological Studies Depressive Scale

CFA: Confirmatory factor analysis

CFI: Comparative Fit Index

CI: confidence interval

CWE: Children with epilepsy

DSM: Diagnostic and Statistical Manual of Mental Disorders

Family APGAR: Family Adaptability, Partnership, Growth, Affection and Resolve

FILE: Family Inventory of Life Events and Changes

FIRM: Family Inventory of Resources for Management

GASE: Global Assessment of Severity of Epilepsy

HERQULES: Health-Related Quality of Life in Children with Epilepsy Study

HRQOL: Health-related quality of life

ICC: intraclass correlation coefficient

LCGM: latent class growth model

M3: Making Mindfulness Matter

MDC: minimal detectable change

PEPSQOL: Pediatric Epilepsy Surgery on Health-Related Quality of Life Study

PSS: Perceived Stress Scale

QOLCE: Quality of Life in Children with Epilepsy Questionnaire

QOLIE-31P: Quality of Life in Epilepsy 31-item

QOLIE-48AD: Quality of Life in Epilepsy-Adolescent 48-item

RMSEA: root mean square of approximation

SEM: standard error of measurement

SF-12: Short-Form health survey

TLI: Tucker-Lewis Index

Chapter 1: Introduction and Research Objectives

1.1 Background

Epilepsy, a condition characterized by spontaneous, unprovoked seizures, is the second most frequent neurological condition (after migraine) [1]. While the long-term prognosis for seizure control is favorable, with 66% to 80% of children attaining seizure control [2,3], it has long been recognized that the impact of epilepsy extends far beyond seizures [4,5]. Up to 80% of children with epilepsy (CWE) have cognitive and/or mental health problems, which significantly impact well-being and life outcomes [6-11]. Therefore, health-related quality of life (HRQOL) is a key outcome considered in treating CWE and is critical in understanding the impact of epilepsy and its treatment. The impact of epilepsy also extends beyond the child, such that families of CWE fare worse relative to healthy families on a variety of factors, such as the quality of the parent-child relationship, parenting confidence, family functioning and stress, and parental psychopathology [5]. Parents of CWE have poorer HRQOL, and recent systematic reviews report that up to 50% and 58% of parents of CWE are at risk for major depression and anxiety, respectively [12-15]. Importantly, poor family environment and parental mental health are not only important for the family's well-being, but have been often shown to have a greater impact on children's health and well-being, relative to epilepsy-related factors [5,9,15-18].

Multiple studies have evaluated long-term seizure outcomes for CWE, however the few long-term studies of CWE's well-being have utilized cross-sectional designs. There have been no studies evaluating any aspect of parental well-being in the long-term. Prospectively delineating the course of children's and parents' well-being from the time of a child's epilepsy diagnosis over the long-term is particularly important in identifying the families at risk for poor outcomes, and providing prognostic information to patients and families to help them prepare for potential long-term outcomes. Although seizures often resolve, epilepsy continues to impact CWE's social

(e.g. employment, romantic relationships) and mental health outcomes in adulthood [19,20]. Prospective studies following CWE and their parents are needed to elucidate the long-term impact of epilepsy on child and parental health and well-being.

Patient self-reports are important in evaluating health outcomes and the impact of the condition and its treatment on functioning. This is especially true for outcomes such as HRQOL and mental health. However, studies focused on children must typically rely on parent-reported measures until children reach a developmental stage where their report is considered appropriate and valid. Additionally, there is often a lack of comparable and validated parent-reported measures for young-adults. Under these circumstances, following young children over the long-term requires that parent reports are utilized in childhood and youth self-reports are utilized in young adulthood. However, delineating trajectories over time using reports from different informants at different time points would potentially introduce bias; this is because child and parent-proxy reports are not interchangeable given that children and parents have unique perspectives and values [21-23]. Although self- and parent-proxy reports are both considered reliable and valid, parents typically report children as having poorer HRQOL and mental health relative to their children's self-report [21-23]. This is a methodological problem in evaluating the HRQOL trajectories of CWE over the long-term and could be addressed by validating and utilizing a parent-reported measure for young-adults. This would allow a consistent informant, the parent, to report at each time point over the long-term. Notably, the validation of parent-reported measure for young-adults does not imply the parent-proxy reports are preferable or a replacement for youth self-reports. Reports from multiple informants, each with unique perspectives and advantages, are ideal and provide an opportunity to better understand clinical problems, their course, their impact, and response to treatments [23].

1.2 Opportunities to Advance Current Knowledge

Although the literature evaluating the role of family environment for child and parent well-being in families with CWE is growing, there have been no studies prospectively evaluating the long-term well-being of CWE, no reviews synthesizing the results of studies evaluating the HRQOL of parents of CWE, and no studies evaluating any aspect of parental well-being in the long-term. Accordingly, the long-term HRQOL trajectories of CWE are unknown, and in addition, it is unknown whether parents of CWE continue to experience poor HRQOL and mental health outcomes in the long-term. It is also unknown which clinical, child, parent, and family factors are associated with the long-term trajectories of well-being for CWE and parents. In addition, there is a need for a psychometrically sound parent-reported measure of HRQOL for CWE for use in prospective cohort studies designed to document long-term trajectories across developmental phases of childhood into emerging adulthood. Addressing these knowledge gaps is the focus of this dissertation.

1.3 Research Objectives

The goals of this dissertation are to prospectively delineate the long-term course and the factors associated with the health and well-being of CWE and their mothers, and to contribute to strengthening the methodological rigor of longitudinal studies for this patient group. Specifically, the objectives of this dissertation are to:

1. Evaluate the psychometric properties of a parent-reported, epilepsy-specific measure of HRQOL, the Quality of Life in Children with Epilepsy (QOLCE) questionnaire, when used by parents to assess the HRQOL of their young adult children.

   a. Evaluate the goodness of fit between the established factor structure of the QOLCE and data from a sample of young adults (ages ≥18 years).
   b. Evaluate the internal consistency of the overall and sub-domain scores of the QOLCE.
   c. Evaluate convergent validity between relevant subscales of the parent-rated QOLCE and self-reported HRQOL, as measured by epilepsy-specific HRQOL instruments.
2. Describe the long-term course of HRQOL in CWE and identify key factors associated with the trajectories of HRQOL.
   a. Describe the course of HRQOL in CWE from epilepsy diagnosis to 0.5, 1, 2, 8, and 10 years later.
   b. Identify the child, parental, and family characteristics at the *time of diagnosis* associated with each trajectory of HRQOL in CWE.
3. Evaluate the long-term HRQOL for mothers of CWE and identify key factors associated with mothers' HRQOL.
   a. Describe HRQOL for mothers of CWE 10 years after their child was diagnosed with epilepsy, relative to population norms.
   b. Identify the child, maternal, and family characteristics at the *time of diagnosis* that are associated with mothers' HRQOL 10-years later.
   c. Identify child, maternal, and family characteristics *at the 10-year follow-up* that are associated with mothers' HRQOL at the 10-year follow-up.
4. Describe the long-term course of depressive symptoms in mothers of CWE, and identify key factors associated with the trajectories of depressive symptoms.

a. Identify the prevalence of risk for major depressive disorder in mothers of CWE 8 and 10 years after their child's diagnosis of epilepsy.
b. Describe the course of mothers' depressive symptoms from the time of their child's epilepsy diagnosis to 0.5, 1, 2, 8, and 10 years later.
c. Identify the child, maternal, and family characteristics at the time of their child's epilepsy diagnosis associated with each trajectory of mothers' depressive symptoms.

Before beginning to address objectives 3 and 4, I conducted a systematic review of quality of life in parents of CWE. The objectives of the review were to 1) systematically review the literature to describe the HRQOL for parents of children with childhood-onset epilepsy, 2) identify the child, parental, and family characteristics associated with parental HRQOL, and 3) evaluate the association between parents' HRQOL and their children's psychological well-being, namely HRQOL, depression and anxiety.

Based on the available empirical evidence from this systematic review and a broader review of the literature (described in subsequent chapters), I formulated three hypotheses related to the thesis objectives regarding long-term well-being for CWE and their mothers:

1. The QOLCE will be validated for parents' assessment of young adults (aged ≥18 years).
2. Distinct trajectories of children's HRQOL will be identified, with the majority of CWE improving over the first two years then plateauing over the long-term. Family characteristics at the time of epilepsy diagnosis will be more strongly associated with HRQOL trajectories than epilepsy-related factors.
3. Ten years after their child's diagnosis of epilepsy, HRQOL of mothers will be poorer relative to population normative data and will be associated with family

characteristics (at baseline and follow-up). Epilepsy-related factors will not be independently associated with mothers' HRQOL in the long-term.

4. Distinct trajectories of mothers' depressive symptoms will be identified, with the majority of mothers showing improvements over the long-term and others following a stable trajectory over time. Family characteristics at baseline, and not epilepsy-related factors, will be associated with trajectories of depressive symptoms.

1.4 How This Dissertation is Structured

This thesis research uses an integrated-article format, with each chapter representing a separate component. Chapter 2 provides a literature review of childhood-onset epilepsy, the HRQOL of children and their parents, and the methodological issues associated with following these children over the long-term. The next five chapters, Chapters 3 to 7, present versions of published articles evaluating Objectives 1 to 4. Chapter 3 reports on methodological work to validate a parent-reported measure of HRQOL for young adults with epilepsy (Objective 1). Chapter 4 delineates the long-term course of CWE's HRQOL and identifies factors associated with HRQOL trajectories (Objective 2). Chapter 5 reports on a systematic review evaluating the HRQOL of parents of children with epilepsy. Chapter 6 evaluates the HRQOL of mothers of CWE in the long-term after their child's epilepsy diagnosis (Objective 3). Chapter 7 describes the long-term course of depressive symptoms in mothers of CWE and identifies factors associated with trajectories of mothers' depressive symptoms (Objective 4). Finally, Chapter 8 provides an overall conclusion and summary of findings, and the implications, limitations and next steps of the research conducted.

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Chapter 2: Literature Review

2.1 Chapter Overview

This chapter provides the context necessary to understand the impact of epilepsy on children and their parents, and highlights the gaps in the extant literature that will be addressed in this dissertation. First, an overview of the clinical presentation of epilepsy is presented, followed by the health-related quality of life (HRQOL) and mental health problems experienced by children with epilepsy and their parents. A conceptual framework is also discussed to better understand and summarize the factors affecting children's and parents' HRQOL and mental health. Lastly, methodological issues associated with prospective evaluations of children over the long-term are discussed.

2.2 Pediatric Epilepsy

Epilepsy, one of the most common neurological conditions, is characterized by an enduring predisposition for epileptic seizures, and by its neurobiologic, cognitive, psychological, and social consequences [1]. Epilepsy is diagnosed when one of the following conditions is met: 1) at least two unprovoked (or reflex) seizures occurring >24 hours apart, 2) one unprovoked (or reflex) seizures and a probability of further seizures similar to the general recurrent risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years, or 3) diagnosis of an epilepsy syndrome [1]. Epileptic seizures are transient periods of altered behavior, including alterations of consciousness and involuntary motor, sensory and autonomic effects, caused by transient abnormal excessive or synchronous neuronal activity. The affected neurons determine the clinical manifestation and subjective experience of a seizure. Seizures are categorized into two types: focal and generalized. Focal seizures originate from a defined region of the brain and

arise from decreased inhibition or increased activation in a group of neurons leading to a net excitatory signal that may then propagate to other regions of the brain [2]. In contrast, generalized seizures involve all, or most of the brain, and are believed to involve alterations to the normal excitatory/inhibitory oscillatory rhythm of the thalamocortical circuit [2]. It is believed that the underlying neural substrate giving rise to seizures also contributes to the cognitive and psychological comorbidities often associated with epilepsy [3].

Worldwide epilepsy affects of 65 million people. Among children and adolescents (≤18 years of age), meta-analyses estimate a cumulative incidence of 85 per 100,000 persons (95%CI: 60, 122), an incidence rate of 47 per 100,000 person years (95% CI: 42, 52), a period prevalence of active epilepsy of 480 per 100,000 persons (95% CI: 417, 552), and a lifetime prevalence of 724 per 100,000 persons (95% CI: 574, 914) [4]. In Canada, epilepsy affects 300,000 persons, of whom 42,000 are children and adolescents; the incidence and prevalence of epilepsy in Canadian children and adolescents (≤18 years of age) are 60 per 100,000 persons and 545 per 100,000 persons, respectively [5]. An estimated 57% of Canadians with epilepsy are diagnosed prior to the age of 19 years [6]. Over the long-term, 60% of children with epilepsy attain seizure control and discontinue antiseizure medications [7,8], however comorbid cognitive and psychological comorbidities may continue to persist and poor social outcomes (e.g. education, employment, romantic relationships) in adulthood are evident [9].

2.3 Comorbidities and Health-Related Quality of Life

Unequivocal evidence has shown that the majority of children with epilepsy (CWE; up to 80%) face cognitive, psychiatric, and/or behavioral comorbidities, many of which continue to go under-recognized and untreated [10-13]. The underlying neuropathology is thought to give rise

to both the characteristics of the epilepsy and the neuropsychological comorbidities [3]. Substantial research has evaluated the HRQOL of CWE, finding poor outcomes across HRQOL domains, including cognitive, emotional, social, and physical functioning [14-17]. Overall, children with newly diagnosed epilepsy have poorer HRQOL relative to normative population data, and over the first two years after diagnosis show initial improvements that plateau with time [18]. However, it is important to note that CWE are a heterogenous group and unique subgroups have been identified that show distinct trajectories of HRQOL, which generally improve over time or remain stable [19-23]. Importantly, these studies have only followed CWE up to the first 28 months following diagnosis, and long-term HRQOL trajectories remain unknown. Although a number of studies have evaluated long-term HRQOL outcomes, all have utilized a cross-section design and have not evaluated HRQOL near the time of epilepsy diagnosis [16,24-27]. Therefore, there is a need for prospective studies evaluating long-term HRQOL trajectories for CWE.

The three studies that have cross-sectionally evaluated long-tern HRQOL have reported on a cohort of participants 9-, [25,26], 10- [28] and >30-years [24] after epilepsy diagnosis. These studies report similar HRQOL among adults with history of epilepsy and healthy controls [24,28] and better HRQOL among those seizure-free [25,26] and seizure-free and not on antiseizure medications [24]. Baca et al. [25,26] evaluated the impact of other clinical characteristics, finding that the presence of a psychiatric disorder, particularly an internalizing disorder, was associated with poorer HRQOL and was a stronger predictor than seizure-control. This finding highlights that HRQOL outcomes are driven by factors beyond seizure-control, a conclusion that is supported by other studies evaluating short-term HRQOL outcomes, as described below.

Studies evaluating HRQOL and mental health problems in the short-term after a diagnosis of epilepsy find that individual- and epilepsy-related factors are not consistent predictors [16,17,29]. Conversely, psychological factors and the response to illness are important; attitude toward illness, external (or unknown) locus of control, hopelessness, limited emotional support, poor family communication, inadequate support of child autonomy, parental psychopathology, and other family factors are commonly associated with children's HRQOL and psychopathology [16,29]. Similar results are found from studies evaluating short-term HRQOL trajectories [19-23]. Past research has also established that family stress and satisfaction with family relationships mediate the negative impact of parental psychopathology on children's HRQOL and emotional well-being, while family mastery and extended family social support moderate this relationship [30-32]. Therefore, in understanding the impact of epilepsy on children, it is important to consider psychosocial factors such as family environment and parental mental health. Section 2.5 presents the conceptual framework used to illustrate the relationships among clinical, parent and family characteristics and their effects on children's HRQOL and mental health. The clinical, parent and family characteristics associated with better long-term HRQOL outcomes are currently unknown and presents a critical knowledge gap. Prospectively delineating the determinants of long-term HRQOL trajectories would allow for the early identification of children at risk of poor outcomes across the life course and provide potential targets for interventions aimed at positively altering trajectories.

2.4 Parents and Families of Children with Epilepsy

Relative to families not living with childhood-onset epilepsy, families of CWE fare worse on the quality of parent-child relationship, parenting confidence, and family relationships,

functioning and stress [33]. Parents of CWE report unmet psychosocial care needs [34], with social and financial burden contributing to parents' feelings of being unable to manage their child's specific needs [35]. Parents report a need for ongoing emotional support and education regarding the emotional and psychological impact that epilepsy may have on their child, as well as difficulty with changes in family roles, unpredictability of seizures, and uncertainty surrounding long-term prognosis [36]. Section 2.5 presents the conceptual framework used to understand and summarise the relationships among clinical, parent, and family characteristics and their effects on parents' HRQOL and mental health. Recent systematic reviews report that up to 50% of mothers and 58% of parents of CWE are at risk for major depression and anxiety, respectively [37,38]. Chapter 5 of this dissertation presents results of a systematic review evaluating HRQOL of parents of children with epilepsy.

Relative to fathers, mothers of CWE have been found to have a poorer quality of life and more symptoms of anxiety, depression, and stress [38-40]; however, it is unclear whether these differences are the result of gender differences or associated with the role of primary caregiver.

Understanding the impact of childhood illness on parents is important for the well-being of both children and parents. Family environment and parental psychopathology are often reported to have a greater impact on CWE's HRQOL and mental health, relative to epilepsy-related factors [18,30,33,37,38,41]. Similarly, parents of children with developmental disabilities and non-neurological chronic conditions, such as asthma, are also at elevated risk for symptoms of depression and anxiety, with family and parent factors identified as robust predictors of well-being, rather than illness characteristics [42-44]. Overall, the long-term mental health outcomes of parents of children with epilepsy are unknown, and there is a need for future studies to delineate long-term outcomes for parents and their determinants.

2.5 Conceptual Framework

The theoretical framework used to guide this research is presented on Figure 2-1. This framework was adapted from the Stress Process Model [45] and aligns with the extant literature evaluating HRQOL and mental health outcomes of children with epilepsy and their parents. The Stress Process Model has been a prevailing conceptual model describing mental health as a consequence of life experience, exposure to stresses, and the social conditions in which one lives [45]. The focus is placed on understanding the relationships among factors contributing to stress and understanding the ways these relationships develop, change, and contribute to mental health. The Stress Process Model contains three main concepts: source of stress, mediating and moderating factors, and the manifestation of stress. First, sources of stress pertain to life events (e.g. diagnosis of epilepsy) and life strains (e.g. living with epilepsy), which develop over longer periods of time. Second, mediating and moderating factors are those that alter the impact that stressors have on mental health outcomes. These psychological resources include social support, coping strategies, family functioning, and stress management strategies. Third, the manifestation of stress can be both physical and mental. In the context of epilepsy, the underlying neuropathology is thought to give rise to stressors: the clinical characteristics such as epilepsy severity and presence of neuropsychological problems, such as cognitive deficits and behavioral and emotional problems. Clinical characteristics impact children's and parents' psychological resources, the stress mediators and moderators, which include family functioning, and children's and parents' social support, coping strategies, and stress management skills. Notably, the clinical characteristics and psychological resources are impacted by and unfold within the context of the child's and parents' sociodemographic characteristics such as age, sex, education and income.

Ultimately the clinical characteristics and psychological resources impact children's and parents' HRQOL and mental health.

2.6 Methodological Issues with Long-term Prospective Studies of Children with Epilepsy

HRQOL is a key patient-reported outcome for people living with chronic conditions, and epilepsy is no exception [46]. However, young children often lack the cognitive maturity and verbal comprehension to provide self reports, so parent-reported outcomes are typically used for young children [47]. Over the course of a long-term study, children 'grow into' developmentally appropriate self-reported measures, and 'grow out of' parent-reported measures. Therefore, longitudinal studies following young children into adulthood are not able to use a consistent informant to assess patient reported outcomes across stages of developments, thereby introducing a potential bias because parents and their children have unique perspectives and values [48]. It is clear from past research that parent-proxy and children's self-reported HRQOL are not interchangeable, with parents of CWE typically reporting poorer HRQOL compared to CWE [47,49,50]. Though this discrepancy may be a consequence of the psychometric properties of the parent and child measures, it is thought that parents and their children have unique, reliable, and valid perspectives on how they rate the child's HRQOL [47,51]. To facilitate methodologically rigorous studies that evaluate the trajectories of children's HRQOL from childhood into adulthood, a consistent informant (e.g. the parent) is needed. A validated parent-reported measure of young adults' HRQOL would offer a way to address this methodological limitation and allow parents to report across their children's stages of development. Although the use of multiple informants is ideal to capture varying relevant perspectives and should be employed

whenever feasible [47], very young children are not capable of providing valid self-reports of HRQOL, and researchers must rely on parent-reports [47].

For CWE, a commonly used measure of HRQOL is the parent-reported Quality of Life in Children with Epilepsy (QOLCE) Questionnaire; an epilepsy-specific 76-item measure for children aged 4-18 years [52,53]. The QOLCE has been shortened and validated, and now includes a 55-item (QOLCE-55)[54] and a 16-item (QOLCE-16)[55] version. Compatible HRQOL measures for other age groups and informants include the self-reported Quality of Life in Epilepsy-Adolescent (48-item; QOLIE-48AD) [56] for adolescents ages 11-17 years, and the self-reported Quality of Life in Epilepsy (31-item; QOLIE-31)[57,58] for adults ages ≥18 years. There are no epilepsy-specific parent-proxy reported HRQOL measures for young adults ages >18 years. Consequently, studies evaluating HRQOL and following young CWE into adulthood must rely on parent-reports at the start of the study, and adolescents' and young adults' (AYA) self-report at later time points even though parents' and their children's reports are not analogous [47,49,50]. Therefore, there is a need for validated instruments to evaluate HRQOL across stages of development, from childhood to young adulthood, using a consistent informant; the parent. The call for such an instrument is not meant to imply that parent-proxy reports of their young adult children's HRQOL are preferable or a replacement for youths' self-report. Reports from multiple informants, each with unique perspectives and advantages, are ideal and provide an opportunity to better understand clinical problems, their course, their impact, and response to treatments [47].

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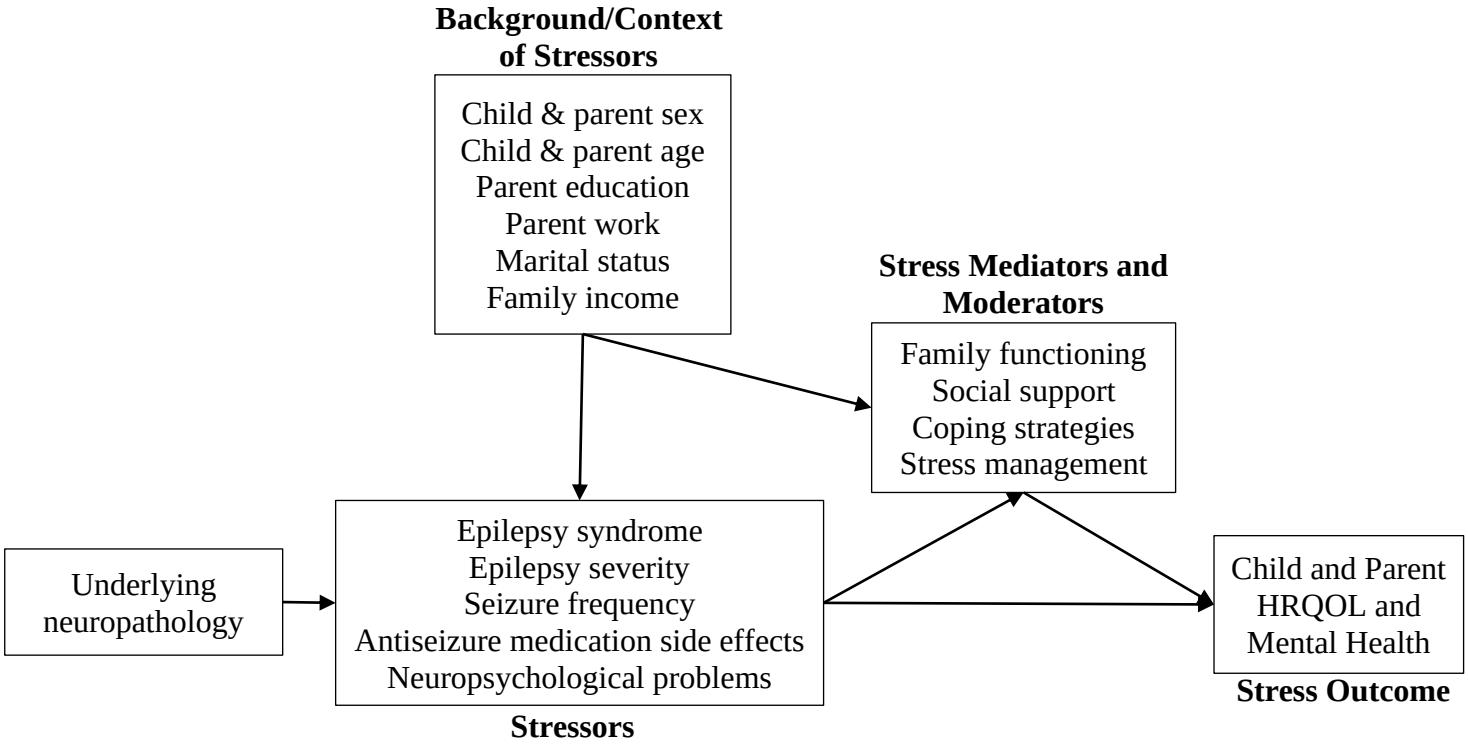
Figure 2-1. Conceptual framework of the impact of clinical and family characteristics on children's and parents' health related quality of life (HRQOL) and mental health, modified from the Stress Process Model.



Chapter 3: Validation of the Quality of Life in Childhood Epilepsy Questionnaire for use by parents of young adults with childhood-onset epilepsy [1]

3.1 Introduction

Health-related quality of life (HRQOL) is a key outcome measure for people with epilepsy and other chronic conditions [1]. Although self-reported measures are preferred, young children lack the cognitive maturity and verbal comprehension capacity to provide self-reports [2]. Consequently, clinicians and researchers working with children must rely on parent-proxy reported HRQOL until children reach a developmental stage where their report is considered appropriate and valid. To reliably evaluate HRQOL for these children over time, a consistent method of measurement is needed, specifically a consistent informant across the child's stages of development and into emerging adulthood. Utilizing parent-proxy reports in early childhood and adolescents' and young adults' (AYA) self-reports in later time points would undoubtedly introduce systematic bias because parent and their children have unique perspectives and their reports are not interchangeable [3]; parents typically report poorer HRQOL for their children compared to the AYA's self-report [2,4-6]. Therefore, to reliably evaluate change from young childhood into emerging adulthood, a consistent informant, the parent, is needed; parent-proxy reports may additionally be augmented by AYA's report to provide a comprehensive account of long-term outcomes and their course since early childhood and disease onset. Additionally, prospective evaluation of long-term HRQOL is particularly important for the early identification of children at risk of poor HRQOL trajectories.

[1] A version of this chapter has been published: Puka K, Goodwin SW, Ferro MA, Smith ML, Widjaja E, Anderson KK, Speechley KN (2020). Validation of the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55 and QOLCE-16) for use by parents of young adults with childhood-onset epilepsy. Epilepsy & Behavior, 104, 106904. DOI: 10.1016/j.yebeh.2020.106904

For children and adolescents with epilepsy, a commonly used measure of HRQOL is the parent-proxy reported Quality of Life in Children with Epilepsy Questionnaire (QOLCE); an epilepsy-specific 76-item measure for those aged 4-18 years [7,8]. The QOLCE was recently shortened and validated, with 55-item (QOLCE-55)[9,10] and 16-item (QOLCE-16)[11] versions available. Similar HRQOL measures with respect to the structure and types of questions are available for other age groups and informants, and include the self-reported Quality of Life in Epilepsy-Adolescent (48-item; QOLIE-48AD) [12] for adolescents ages 11-17 years, and the self-reported Quality of Life in Epilepsy (31-item; QOLIE-31-P)[13,14] for adults ages ≥18 years. Lastly, the PedsQL Epilepsy module was recently validated for children and adolescents aged 2-18 years by parent-proxy report and ages 5-18 by self-report [15]. Notably, there are no epilepsy-specific parent-proxy reported HRQOL measures for young adults ages >18 years. Research assessing the viability of extending the use of a parent-proxy reported HRQOL measure into the period of emerging adulthood for children with epilepsy have not been conducted previously.

The objective of this study was to evaluate the psychometric properties of the parent-proxy reported QOLCE (QOLCE-55 and QOLCE-16) when used by parents to assess HRQOL in their children as young adults. Specifically, within a sample of young adults with childhood-onset epilepsy, we aimed to a) evaluate the goodness of fit of the established factor structure of the QOLCE; b) evaluate the internal consistency of the overall and sub-domain scores of the QOLCE; and c) evaluate the convergent validity between similar subscales of the parent-proxy rated QOLCE and the AYA self-reported QOLIE-31-P. Importantly, the purpose of this research was not to imply that parent-proxy -report of their adult children's HRQOL is preferable and a replacement for AYA's self-report. Reports from multiple informants, each with unique

perspectives and advantages, are ideal and provide an opportunity to better understand clinical problems, their course, their impact, and response to treatments [2].

3.2 Methods

3.2.1 Participants

Data for this study were obtained from four sources, outlined below. From each source, young adults aged ≥18 years and data from the last follow-up assessment, if multiple assessments were eligible for inclusion, were extracted. Combining results from four Canadian data sources is advantageous in increasing the sample size and producing results generalizable to a wider array of individuals with childhood-onset epilepsy. Approval was obtained from all relevant research ethics boards.

3.2.1.1 Data Source 1: HERQULES. The Health-Related Quality of Life in Children with Epilepsy Study (HERQULES) is a prospective cohort study of children with newly-diagnosed epilepsy, with assessments at the time of diagnosis and 0.5, 1, 2, 8, and 10 years post-diagnosis. The study has been described in detail previously [16]. Briefly, pediatric neurologists across Canada were invited to participate and they consecutively recruited their patients meeting inclusion criteria. Eligible children were 4 to 12 years of age with newly diagnosed epilepsy (≥2 unprovoked seizures) and seen for the first time by a participating pediatric neurologist. Children were not eligible if they also had a diagnosis of other progressive or degenerative neurological disorders, or other major comorbid non-neurological health condition likely to have an impact on HRQOL (e.g., asthma requiring daily medication, renal failure). The primary caregiving parent completed questionnaires at each time point, and AYA completed questionnaires at the 8- and 10-year follow-up. For this report, we utilized data from the last available follow-up, at either the 8- or 10-year follow-up.

3.2.1.2 Data Source 2: PEPSQOL. The Impact of Pediatric Epilepsy Surgery on Health-Related Quality of Life Study (PEPSQOL), is a prospective cohort study of children (aged 4 to 18 years) with drug-resistant epilepsy undergoing evaluations to determine candidacy for epilepsy surgery. The study has been described in detail previously [17]. Data were collected from nine surgical epilepsy centers across Canada, and exclusion criteria included: 1) prior resective surgery, past or planned non-resective epilepsy surgery (e.g. corpus callosotomy) or vagal nerve stimulator placement; 2) neurometabolic disorders, neurodegenerative disorders, and genetic epilepsy syndromes; and 3) primary generalized epilepsy and epileptic encephalopathies. Patients who were not able to complete self-report questionnaires, either independently or with assistance, were also excluded. AYA were eligible for the study irrespective of whether they underwent epilepsy surgery. Nonsurgical patients include patients that chose not to undergo surgery and patients ineligible for surgery because a clear unilateral seizure focus could not be identified or the benefits of surgery were not outweighed by deficits that would have arisen subsequently. A number of studies have shown that surgical and nonsurgical groups are similar at the time of surgical evaluation on a number of cognitive and psychosocial factors [18,19]. Data collection occurred at the time of surgical evaluation and 0.5, 1, and 2 years after a) the surgical evaluation (for nonsurgical patients) or b) epilepsy surgery (for surgical patients). Parents and their children completed questionnaires at each time point. For this report, we utilized data from the last available follow-up, at which point some patients had undergone epilepsy surgery (see Table 3-1).

3.2.1.3 Data Source 3: Epilepsy Surgery Outcomes Study. This study evaluated long-term outcomes of children with drug-resistant epilepsy, and has been described in detail previously [20,21]. Eligible participants underwent epilepsy surgery evaluations at the Hospital for Sick Children in Toronto, Canada, and were 18 years or younger at that time. Patients who did and did

not subsequently undergo epilepsy surgery were included. Multiple cognitive, behavioral, and social outcomes were evaluated at the time of surgical candidacy evaluation and 4 to 11 years after a) the surgical candidacy evaluation (for nonsurgical patients) or b) epilepsy surgery (for surgical patients). Exclusion criteria included hemispherectomy, corpus callosotomy or vagal nerve stimulation procedures, and patients with neurodegenerative disorders. Parents and their children completed questionnaires at each time point. For this report, we utilized data from the last available follow-up, at which point some patients had undergone epilepsy surgery (see Table 3-1).

3.2.1.4 Data Source 4: Clinic Sample. Data were collected from medical records of patients with drug-resistant epilepsy evaluated for epilepsy surgery at the Hospital for Sick Children [18,19]. At the time of surgical evaluation children were aged ≤18 years, and as part of clinical care patients were followed for a minimum of one-year past surgery. Child and clinical factors were extracted from patient charts, which included measures of HRQOL. For this report, we utilized data from the last available follow-up, at which point some patients had undergone epilepsy surgery (see Table 3-1).

3.2.2 Measures

The primary measures of interest were the 55-item and 16-item versions of Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55 [9,10,22] and QOLCE-16 [11,23]). The QOLCE-55 was derived from the questions of the original 76-item QOLCE [7,8], and the QOLCE-16 was derived from the questions of the QOLCE-55. Parents had completed the 76-item QOLCE and data for the QOLCE-55 and QOLCE-16 were extracted. Both versions generate an overall HRQOL score, and scores for four sub-domains: cognitive, emotional, social, and physical functioning. Scores range from 0 to 100, with higher scores indicative of better

HRQOL. The primary caregiving parent completed the QOLCE and questions pertaining to demographic and clinical characteristics.

Young adults completed the self-reported Quality of Life in Epilepsy questionnaire (QOLIE-31-P) [13,14]; these data were only available from the HERQULES and the Epilepsy Surgery Outcomes Study. The QOLIE-31-P is an epilepsy-specific measure of HRQOL, composed of 31-items evaluating overall HRQOL and mood (i.e. emotional functioning), daily activities (i.e. social functioning), cognition (i.e. cognitive functioning), energy/fatigue, seizure worry, and medication effects over the past four weeks [13,14]. Scores range from 0 to 100, with higher scores indicative of better HRQOL. The QOLIE-31 has been reported to be internally consistent with Cronbach alpha coefficients for the overall score of 0.93 and 0.77 to 0.85 for the subscales [13]. Test-retest reliability coefficients reported for the QOLIE-31 are 0.89 for the overall score and a range of 0.64 to 0.85 for the subscales [13].

3.2.3 Data Analysis

Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and Mplus 6.12 (Muthen & Methun, 1998-2011) and were completed separately for the QOLCE-55 and QOLCE-16. We excluded participants for whom a total QOLCE score could not be generated because of missing data ($n_{QOLCE-55} = 19$ and $n_{QOLCE-16} = 10$). Given that the QOLCE-16 has fewer items, more participants had complete QOLCE-16 data as compared with the QOLCE-55.

Confirmatory factor analysis (CFA) was used to assess the construct validity of the parent-proxy reported QOLCE for young adults with childhood-onset epilepsy. CFA allows for an estimation of the goodness of fit between the sample data and the established factor structure of the QOLCE (Figure 3-1). The established factor structure of the QOLCE is composed of a four-factor solution and a higher-order factor, whereby each item loads to a single factor

(cognitive, emotional, social, or physical functioning), and the four-factors load onto a single higher order factor, overall HRQOL [9,11]. Robust weighted least square estimator with delta parameterization was used. Adequacy of model fit was evaluated using conventional criteria, namely the Comparative Fit Index (CFI; acceptable >0.90); Tucker-Lewis Index (TLI; acceptable >0.90); and root mean square of approximation (RMSEA; acceptable <0.08) [24-28]. The chi-square test was not used for decisions of model fit because it is sensitive to sample size [24].

Reliability of the scales for the overall score and four sub-domains of the QOLCE was evaluated using Cronbach's alpha and the greatest lower bound (glb)[29], with coefficients of >0.70 considered satisfactory. Convergent validity was evaluated using intraclass correlation coefficient (ICC), which account for differences in means-between subscales of the QOLCE and the self-reported QOLIE-31-P purporting to assess the same construct. Specially, we evaluated the correlation between the QOLCE overall HRQOL and the QOLIE-31-P overall HRQOL; QOLCE cognitive functioning and QOLIE-31-P cognition; QOLCE emotional functioning and QOLIE-31-P mood; and QOLCE social functioning and QOLIE-31-P daily activities. ICC was calculated using a one-way random effects model, absolute agreement, and single measurement [30], and was interpreted as poor to fair (≤.40), moderate (0.41 – 0.60), good (0.61 – 0.80), or excellent (>0.80).

We could not evaluate convergent validity of the QOLCE physical functioning subscale because a corresponding subscale is not available in the QOLIE-31-P. The QOLCE physical functioning subscale evaluates restrictions in physical activities (e.g. How often has your child: *'Been able to do the physical activities other children his/her age do?'; 'Played freely outside the house like other children his/her age?')*. The energy subscale of the QOLIE-31-P is the most similar subscale to QOLCE physical functioning, though the included questions are substantively

different, asking '*Did you feel full of pep?*', '*Did you have a lot of energy?*', '*Did you feel worn out?*', and '*Did you feel tired?*'. While the original 76-item QOLCE contained an energy/fatigue subscale, these items were removed in the development of the QOLCE-55 and QOLCE-16.

3.3 Results

A total of 123 QOLCE-55 and 134 QOLCE-16 were completed. At the time of participation, their children (50% female) were aged 18.0 to 28.5 years, and 68% had been seizure-free for the past 12 months (see Table 3-1). Participants were aged 1.5 months to 16.0 years at the time of epilepsy onset, and 31% had previously undergone epilepsy surgery.

3.3.1 Higher-order Factor Structure

3.3.1.1 QOLCE-55

Results from the confirmatory factor analysis for the QOLCE-55, representing the summary of the higher-order structure, are presented in Table 3-2. The model showed acceptable fit: CFI = 0.968, TLI = 0.966, and RMSEA = 0.061 (95% confidence interval [CI]: 0.056, 0.067). The standardized parameter estimates for the first-order items are presented in Table 3-3; all items loaded significantly onto their respective first-order factors ($p \leq 0.01$). The four-first order factors (cognitive, emotional, social, and physical functioning) loaded onto a single higher-order factor (overall HRQOL). Higher order factor loadings were strong, ranging from $\lambda = 0.71$ to 0.88 ($p < 0.001$).

For one item in the physical functioning sub-domain (item #48 in Table 3-3), the standardized factor loading was 1.10 and the residual variance was -0.22. Removal of this item resulted in similar model fit: CFI = 0.971, TLI = 0.970, RMSEA = 0.059 (95% CI: 0.053, 0.064) and minimal impact to total HRQOL and physical functioning scores; the mean change in overall

HRQOL and physical functioning was 0.21 (95% CI: 0.08, 0.35) and 0.90 (95% CI :0.28, 1.51), respectively. Because of the minimal impact, results with this item retained are included in Table 3-2.

3.3.1.2 QOLCE-16

Results of the confirmatory factor analysis for the QOLCE-16, representing the higher-order structure are presented in Table 3-2. The model showed adequate fit: CFI = 0.966, TLI = 0.959, and RMSEA = 0.141 (95% CI: 0.126, 0.157). The standardized parameter estimates for the first-order items are presented in Table 3-3; all items loaded significantly onto their respective first-order factors ($p < 0.001$). Higher order factor loadings were strong, ranging from $\lambda = 0.76$ to 0.90 ($p < 0.001$).

For one item in the physical functioning sub-domain (item #48 in Table 3-3) the standardized factor loading was 1.05 (residual variance: -0.09). As was found in QOLCE-55, removal of this item resulted in similar model fit: CFI = 0.977, TLI = 0.972, RMSEA = 0.124 (95% CI: 0.107, 0.141), and minimal impact on total HRQOL and physical functioning scores; difference in scores was -0.25 (95% CI: -0.62, 0.12) and -1.37 (95% CI: -2.67, -0.07), respectively. Because of the minimal impact, results with this item retained are included in Table 3-2.

3.3.2 Internal Consistency and Convergent Validity

3.3.2.1 QOLCE-55

The internal consistency/reliability of the QOLCE-55 was excellent for overall HRQOL and good to excellent for each subscale; alpha/glb values were: 0.97/0.99 for overall HRQOL, 0.98/0.99 for cognitive, 0.92/0.96 for emotional, 0.94/0.95 for social, and 0.89/0.95 for physical functioning. Convergent validity was examined via ICC comparing similar domains from the

parent-proxy -reported QOLCE-55 and the self-reported QOLIE-31-P. Of primary interest, the correlation between overall HRQOL as reported by parents on the QOLCE-55 and young adults on the QOLIE-31-P was good (ICC=0.76; 95% CI 0.64 - 0.85; n = 65). The correlations were moderate to good between the parent-proxy reported QOLCE-55 and the self-reported QOLIE-31-P on the domains of cognitive (ICC=0.61; 95% CI 0.44 - 0.74; n = 65), emotional (ICC=0.59; 95% CI 0.40 - 0.73; n = 65), and social functioning (ICC=0.78; 95% CI 0.65 - 0.86; n = 56).

3.3.2.2 QOLCE-16

The internal consistency/reliability of the QOLCE-16 was excellent for overall HRQOL and good to excellent for each subscale; alpha/glb values were: 0.93/0.98 for overall HRQOL, 0.93/0.95 for cognitive, 0.87/0.88 for emotional, 0.95/0.95 for social, and 0.78/0.87 for physical functioning. With respect to convergent validity of the QOLCE-16, the correlation between overall HRQOL as reported by parents on the QOLCE-16 and young adults on the QOLIE-31-P was good (ICC=0.72; 95% CI 0.59 - 0.82; n = 72). The correlations were moderate to good between the parent-proxy reported QOLCE-16 and the self-reported QOLIE-31-P on the domains of cognitive (ICC=0.51; 95% CI 0.31 - 0.66; n = 72), emotional (ICC=0.55; 95% CI 0.37 - 0.69; n = 71), and social functioning (ICC=0.68; 95% CI 0.51 - 0.79; n = 60).

3.4 Discussion

The current study aimed to validate the QOLCE for young adults with epilepsy to allow for reliable assessments of HRQOL over time, from early childhood through emerging adulthood. Overall, the results suggest that the QOLCE-55 and QOLCE-16 are reliable and valid instruments that can be used to reliably evaluate HRQOL over time and into adulthood. Validated prospective accounts of HRQOL by parents, in conjunction with AYA's self-report

provides a comprehensive account of HRQOL at disease onset and over the long-term, allowing for the identification of early predictors of HRQOL trajectories.

The higher-order factor structure of both the QOLCE-55 and QOLCE-16 was confirmed in a sample of young adults with a history of childhood-onset epilepsy. All items on the questionnaires loaded significantly onto their respective domains. The same single item on both the QOLCE-55 and QOLCE-16 ('*Needs more supervision than other children his/her age?*') was found to have a standardized factor loading greater than 1 (and a negative residual variance). However, we do not believe that this undermines the validity of the QOLCE-55 and QOLCE-16 for young adults for several reasons. The factors in the QOLCE-55 and QOLCE-16 are correlated with each other. Past research has shown that models with correlated factors can produce, in certain situations, item factor loadings having values greater than one, without being indicative of a model or structural issue [31]. Given that this single item in the QOLCE does not impact the model fit or estimation of loadings for the overall higher-order structure, we suggest that the higher standardized factor loading is not a concern for the overall validity of the measure. Furthermore, individual item scores from the QOLCE are not used in evaluating outcomes and removal of the item resulted in negligible changes in the model and overall HRQOL and physical functioning scores.

It is important to note that the aim of this study was not to suggest that parent-proxy reports of HRQOL in adults should be routinely used, but rather to present a valid method of measuring HRQOL longitudinally from early childhood with a consistent method and informant. Although the QOLCE-55 and QOLCE-16 may also be utilized by cross-sectional studies of young adults, it is important that self-reported HRQOL is also obtained whenever possible. Parents and their children have unique perspectives on well-being, and children's and AYA's reports are not interchangeable with those of their parents, who typically report poorer HRQOL

relative to self-reports [2,4,5]. The use of multiple informants to capture varying relevant perspectives is therefore ideal and recommended [2].

We also evaluated internal consistency, which were acceptable for overall HRQOL and each subscale of the QOLCE-55 and QOLCE-16. Convergent validity of the QOLCE-55 and QOLCE-16 were also assessed, comparing parents' reports with young adult's self-reports on the QOLIE-31-P. Overall, results were acceptable, showing moderate to high correlations, for overall HRQOL, as well as the domains of cognitive, emotional and social functioning. In line with past studies, we also found greater agreement between parents and their children with respect to more externalized domains, such as social functioning, relative to more internalized domains, such as emotional functioning [2,4,5].

Several limitations of this study should be considered. Although we aimed to increase sample size and generalizability by including a wide array of young adults with childhood-onset epilepsy, the resulting sample size may be considered small for confirmatory factor analysis research. In addition, we did not have data to evaluate test-retest reliability, and a subset of the sample was used to evaluate construct validity. Therefore, further evaluation of the validity of the QOLCE-55 and QOLCE-16 is encouraged for other studies with larger samples of young adults with a history of childhood-onset epilepsy. Given the relatively small number of patients from each data source, we could not evaluate whether model fit was different among the four data sources, although model fit of the largest sample alone (the HERQULES data) yielded similar results (data not shown). In addition, limited demographic and clinical characteristics were consistently available in each of the datasets combined for analyses, thus precluding a more detailed description of our sample on characteristics such as the presence of comorbidities. In addition, we did not have information pertaining to the young adults' living arrangements and whether they resided with their parents. Though this is an important topic for future research, the

results of the present study provide the first step in validating a tool to be used by the clinician's and/or researchers' discretion and best used to supplement young adults' self-reported HRQOL. Lastly, a potential criticism of the QOLCE is that it is focused on *function*, as opposed to *satisfaction* in different domains [2]. The focus on function may help parents more accurately rate items as they believe their child would rate them. Additionally, reports from multiple informants are ideal and provide an opportunity to better understand clinical problems, their course, their impact, and response to treatments [2]. In conclusion, the present findings support the use of the QOLCE-55 and QOLCE-16 as a reliable and valid parent-proxy reported instruments for young adults with a history of childhood-onset epilepsy. This capability may facilitate the evaluation of long-term trajectories of HRQOL from childhood into emerging adulthood employing measurement by a consistent informant. Self-reported measures of HRQOL remain an integral part of evaluating young adults' HRQOL, and reports from multiple informants may be further valuable in providing varying perspectives. Furthermore, there is a need to develop self-reported epilepsy-specific HRQOL measures that can be adapted for use as children mature through childhood, adolescents, and adulthood.

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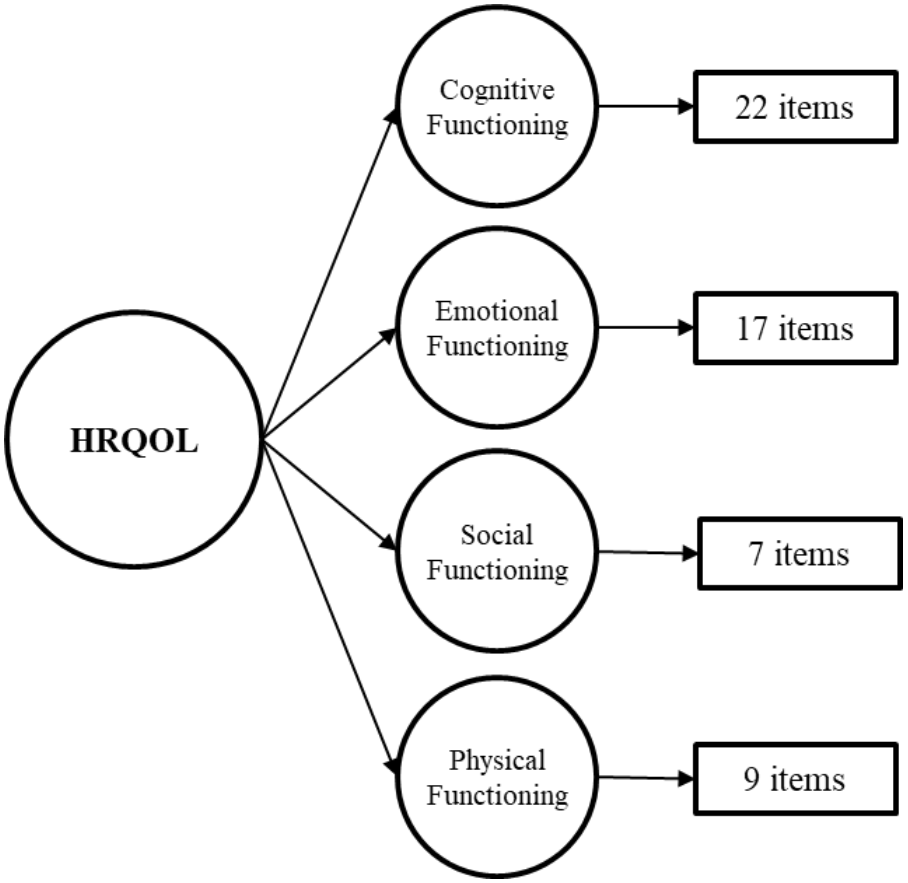
Figure 3-1. Summary of the established factor structure of the Quality of Lifein Childhood Epilepsy Questionnaire (QOLCE-55).



HRQOL: Health-related quality of life.

Table 3-1. Participant characteristics of young adults with data available for the QOLCE-55 and QOLCE-16.

		Data Source			
	Complete Sample	HERQULES	PEPSQOL	Surgery Outcomes Study	Clinic Sample
QOLCE-55					
Sample size	123	69	25	17	12
Age at epilepsy onset, years [a]	9.1 (3.6)	9.9 (1.4)	8.9 (5.0)	5.6 (4.5)	9.9 (5.0)
Age, years	20.2 (2.0)	20.3 (1.5)	18.7 (0.8)	22.9 (2.9)	18.7 (0.4)
Sex, female [b]	59 (50%)	32 (46%)	12 (48%)	11 (64%)	4 (50%)
Underwent epilepsy surgery	38 (31%)	0 (0%)	14 (56%)	12 (71%)	12 (100%)
Seizure-free > 1-year [c]	79 (68%)	57 (86%)	13 (56%)	5 (29%)	4 (36%)
QOLCE-16					
Sample size	134	76	25	18	15
Age at epilepsy onset, years [a]	9.1 (3.6)	9.9 (1.4)	8.9 (5.0)	6.0 (4.8)	8.9 (5.0)
Age, years	20.1 (2.0)	20.3 (1.5)	18.7 (0.8)	22.8 (2.9)	18.6 (0.4)
Sex, female [b]	64 (50%)	36 (47%)	12 (48%)	12 (67%)	4 (40%)
Underwent epilepsy surgery	41 (31%)	0 (0%)	14 (56%)	13 (72%)	14 (93%)
Seizure-free > 1-year [c]	87 (68%)	63 (86%)	13 (56%)	6 (33%)	5 (36%)

Missing data for [a]1 patient, [b]5 patients, [c]6 patients.
Mean (SD) or n (%) are presented.

Table 3-2. Summary of the higher-order summary factor model of the QOLCE-55 and QOLCE-16. For simplicity, first-order items were not included.

	QOLCE-55			QOLCE-16		
	Factor loading (SE)	R^2 (SE)	Residual error	Factor loading (SE)	R^2 (SE)	Residual error
Cognitive Functioning	0.86 (0.03)	0.77 (0.06)	0.26	0.78 (0.05)	0.60 (0.08)	0.40
Emotional Functioning	0.88 (0.04)	0.69 (0.07)	0.22	0.83 (0.05)	0.69 (0.77)	0.31
Social Functioning	0.85 (0.04)	0.82 (0.03)	0.28	0.90 (0.04)	0.80 (0.07)	0.20
Physical Functioning	0.71 (0.05)	0.43 (0.08)	0.50	0.76 (0.05)	0.58 (0.07)	0.42

Standardized factor loading are shown and all were significant at $p < 0.001$. SE: Standard Error

Table 3-3. Standardized parameter estimates for first-order items.

	QOLCE-55		QOLCE-16	
	Factor loading (SE)	R^2 (SE)	Factor loading (SE)	R^2 (SE)
Cognitive Functioning				
1. Had trouble understanding directions?	0.92 (0.02)	0.84 (0.03)	0.95 (0.01)	0.91 (0.03)
2. Had difficulty following complex instructions?	0.94 (0.01)	0.88 (0.03)	0.97 (0.01)	0.94 (0.03)
3. Had trouble understanding or following what others were saying?	0.94 (0.01)	0.89 (0.03)		
4. Had difficulty following simple instructions?	0.90 (0.02)	0.81 (0.04)	0.95 (0.01)	0.91 (0.03)
5. Had trouble remembering things people told him/her?	0.88 (0.02)	0.77 (0.04)	0.84 (0.03)	0.71 (0.05)
6. Had trouble finding the correct words?	0.89 (0.02)	0.79 (0.04)		
7. Found it hard remembering things?	0.89 (0.02)	0.78 (0.04)		
8. Had trouble concentrating on a task?	0.88 (0.02)	0.78 (0.04)		
9. Had trouble remembering things s/he read hours or days before?	0.92 (0.02)	0.85 (0.03)		
10. Had difficulty doing one thing at a time?	0.77 (0.04)	0.59 (0.06)		
11. Had difficulty reasoning or solving problems?	0.91 (0.02)	0.82 (0.04)		
12. Had trouble understanding what s/he read?	0.93 (0.02)	0.86 (0.03)		
13. Reacted slowly to things being said and done?	0.88 (0.03)	0.78 (0.05)		
14. Had difficulty keeping track of conversations?	0.94 (0.02)	0.88 (0.03)		
15. Had trouble remembering names of people?	0.81 (0.03)	0.66 (0.06)		
16. Had trouble remembering where s/he put things?	0.75 (0.04)	0.57 (0.06)		
17. Had difficulty concentrating on reading?	0.90 (0.02)	0.80 (0.04)		
18. Planned to do something than forgot?	0.78 (0.04)	0.61 (0.06)		
19. Had difficulty making plans or decisions?	0.90 (0.02)	0.80 (0.04)		
20. Had trouble writing?	0.76 (0.04)	0.58 (0.06)		
21. Had trouble talking?	0.83 (0.03)	0.69 (0.05)		
22. Had difficulty attending to an activity	0.84 (0.03)	0.71 (0.06)		
Emotional Functioning				
23. Felt no one cared?	0.84 (0.04)	0.71 (0.07)		
24. Wished s/he was dead?	0.62 (0.08)	0.38 (0.10)		
25. Felt nobody understood him/her?	0.89 (0.03)	0.80 (0.05)	0.89 (0.03)	0.80 (0.05)
26. Angered easily	0.73 (0.05)	0.53 (0.08)		
27. Hit or attacked people	0.59 (0.10)	0.35 (0.12)		
28. Felt happy?	0.77 (0.04)	0.59 (0.06)		
29. Felt down or depressed?	0.78 (0.04)	0.61 (0.06)	0.79 (0.03)	0.62 (0.05)
30. Swore in public	0.42 (0.09)	0.18 (0.08)		
31. Felt frustrated?	0.83 (0.04)	0.68 (0.07)	0.84 (0.05)	0.70 (0.08)
32. Demanded a lot of attention?	0.84 (0.05)	0.71 (0.08)		
33. Was socially inappropriate (said or did something out of place in a social situation)?	0.85 (0.05)	0.72 (0.09)		
34. Felt valued?	0.80 (0.04)	0.64 (0.06)		
35. Worried a lot?	0.70 (0.05)	0.49 (0.07)		
36. Was obedient?	0.46 (0.06)	0.21 (0.06)		
37. Felt pleased about achieving something?	0.64 (0.06)	0.41 (0.07)		
38. Felt excited or interested in something?	0.78 (0.04)	0.60 (0.06)		
39. Felt confident?	0.81 (0.04)	0.66 (0.06)	0.84 (0.04)	0.70 (0.08)
Physical Functioning				
40. Gone to parties without you or without supervision?	0.90 (0.03)	0.81 (0.05)		
41. Stayed out overnight (with friends or family)?	0.74 (0.06)	0.54 (0.08)		
42. Played with friends away from you or your home?	0.98 (0.02)	0.96 (0.05)		
43. Played freely in the house like other children his/her age?	0.47 (0.08)	0.23 (0.08)	0.60 (0.07)	0.35 (0.08)
44. Participated in sports activities (other than swimming)?	0.56 (0.09)	0.32 (0.10)		
45. Been able to do the physical activities other children his/her age do?	0.81 (0.06)	0.65 (0.09)	0.77 (0.05)	0.60 (0.08)
46. Played freely outside the house like other children his/her age?	0.74 (0.07)	0.54 (0.10)	0.83 (0.05)	0.69 (0.09)

47. Gone swimming? (i.e., swam independently)	0.32 (0.12)	0.10 (0.08)		
48. Needs more supervision than other children his/her age?	1.10 (0.05)	-	1.05 (0.04)	-
Social Functioning				
49. Limited his/her social activities (visiting friends, close relatives, or neighbors)?	0.91 (0.04)	0.82 (0.06)		
50. Limited his/her leisure activities (hobbies or interests)?	0.74 (0.06)	0.55 (0.08)		
51. How limited are your child's social activities compared with others his/her age?	0.91 (0.03)	0.84 (0.05)	0.91 (0.03)	0.83 (0.05)
52. Affected his/her social interactions at school or work?	0.93 (0.03)	0.86 (0.05)	0.92 (0.02)	0.85 (0.04)
53. Isolated him/her from others?	0.97 (0.02)	0.93 (0.03)	0.98 (0.01)	0.95 (0.03)
54. Made it difficult for him/her to keep friends	0.94 (0.02)	0.89 (0.04)	0.95 (0.02)	0.90 (0.04)
55. Frightened other people?	0.90 (0.04)	0.81 (0.08)		

All p-values were significant at $p < 0.001$ (except QOLCE-55 item #47, where $p = 0.01$); SE: Standard error

Chapter 4: Long-term quality of life trajectories among individuals diagnosed with epilepsy in childhood [1]

4.1 Introduction

The majority of children with epilepsy face cognitive, psychiatric, and/or behavioral comorbidities that often to go under-recognized and untreated[1-4]. Furthermore, although seizures often resolve over the long-term, epilepsy continues to impact social outcomes in adulthood (e.g. education, employment, romantic relationships)[5]. Understandably, health-related quality of life (HRQOL) is a key outcome for individuals with epilepsy and is critical for understanding the impact of epilepsy and its treatment. In one of the first comprehensive prospective studies of HRQOL, our group showed that children with epilepsy have poorer HRQOL in comparison to their similarly-aged peers at the time of diagnosis, and show some improvements over the following two years that plateaus with time[6]. Further work by our group demonstrated that children with epilepsy are heterogenous and experience several distinct trajectories of HRQOL, which generally improve over time or remain stable over the first two years after diagnosis[7,8]. These findings were important in providing a comprehensive evaluation of HRQOL and its determinants over the first two years after an epilepsy diagnosis in childhood, but describing a relatively short, two-year window leaves unanswered questions for clinicians and families about what the longer-term future holds for these children. Therefore, in the current study, we present the results from an extended 10-year follow-up of this same cohort of children.

[1] A version of this chapter has been published: Puka K, Ferro MA, Camfield CS, Levin SD, Smith ML, Wiebe S, Zou G, Anderson KK, Speechley KN (2020). Trajectories of quality of life 10 years following a diagnosis of epilepsy in childhood. Epilepsia 61, 1453-1463. DOI: 10.1111/epi.16579

A major limitation of previous prospective studies of children's HRQOL has been their relatively short follow-up of 24 to 28-months[6-11]. Virtually no information is available on HRQOL over the long-term, including whose HRQOL will likely improve, remain the same or decline over time and for what reasons, especially as these children become adolescents and young adults (AYAs). Only two studies have investigated long-term HRQOL[12-14]. Conclusions to be made from these studies are limited by cross-sectional study designs, precluding the investigation of risk factors and their limited focus on characteristics associated with HRQOL; these studies have focused on clinical and demographic characteristics which are not associated with short-term HRQOL and mental health outcomes, with the exception of seizure-control [15-17]. There have been no long-term investigations including other categories of known risk factors for HRQOL such as families' resources to deal with a child's chronic illness, other stressors in their lives, child-family interactions and relationships, and parent mental health. As well, there is no information regarding the stability of predictors at observable at diagnosis on long-term HRQOL. Lastly, adolescence is a time of tremendous physical, mental, and social change and adolescents with epilepsy may be at particular risk for compromised HRQOL as they mature towards adulthood. Therefore, there is a tremendous need to better understand trajectories of HRQOL for children diagnosed with epilepsy as they develop into AYAs and the clinical, parent, and family factors that are key risk and protective factors. Prospectively delineating the course of children's long-term HRQOL and its determinants would also allow for the early identification of children at risk of poor outcomes across the life course as potential targets for resources aimed at positively altering trajectories.

The objective of this study was to describe the long-term course (10-year follow-up) of HRQOL among children with newly diagnosed epilepsy and identify key characteristics at diagnosis associated with the trajectories of HRQOL. Specifically, we aimed to evaluate 1)

whether the improvement in HRQOL scores observed over the first two years after diagnosis continues as children mature into young adults, 2) whether the individual and family-level characteristics that predicted short-term HRQOL (i.e. child cognitive problems, maternal depression, and high family demands) have longer term prognostic power or whether other factors have more prominence later in the course of the illness. These questions have not been previously investigated for any patient-reported outcome, such as HRQOL, for children with epilepsy and the answers are important for clinicians, patients, and families to better understand the long-term course of pediatric epilepsy, beyond seizure control.

4.2 Methods

4.2.1 Participants and Study Design

Participants came from a population-based study of children with newly-diagnosed epilepsy, the Health-Related Quality of Life in Children with Epilepsy Study (HERQULES) [6]. Participants were recruited by pediatric neurologists across Canada between April 2004 and April 2007. Participating neurologists were asked to consecutively recruit all patients meeting study inclusion criteria: children aged 4 to 12 years with newly diagnosed epilepsy (≥2 unprovoked seizures) and seen for the first time by a participating pediatric neurologist. The lower age limit was chosen because there were no epilepsy-specific HRQOL measures available for children under the age of 4 years. Exclusion criteria included a diagnosis of other progressive or degenerative neurological disorders, or other major comorbid non-neurological health condition likely to have an impact on HRQOL (e.g., asthma requiring daily medication, renal failure). Ethics approval was obtained from relevant research ethics boards, and parents provided written consent.

A total of 456 eligible children were identified, and the parents of 373 (82%) returned baseline questionnaires mailed to them. All measures described below were completed at the time of epilepsy diagnosis (baseline) and at 0.5, 1, 2, 8, and 10-year follow-ups by the primary caregiving parent or the child's neurologist.

4.2.2 Measures

4.2.2.1 Children's Health-related Quality of Life

Children's HRQOL was evaluated using the parent-reported, Quality of Life in Childhood Epilepsy Questionnaire (QOLCE). Scores on the 55-item QOLCE are reported given that it has been validated for use by parents for children/adolescents [18-20] and young adults [21] with epilepsy. The QOLCE-55 generates an overall HRQOL score ranging from 0 to 100, with higher scores indicative of better HRQOL. In this study, the internal consistency of the QOLCE-55, measured using Cronbach's alpha ranged from 0.96 to 0.97.

4.2.2.2 Demographic and Clinical Characteristics

Parents reported on their child's age and sex, and at the 8- and 10-year follow-up were asked about their child's most recent seizure and if their child was ever diagnosed with cognitive problems (developmental delay or learning disability), behavioral problems (conduct disorder, oppositional defiant disorder, or attention deficit hyperactivity disorder), emotional problems (anxiety or depression), or autism spectrum disorder. Pediatric neurologists reported on epilepsy/syndrome classification, severity of epilepsy, and the presence of behavioral, cognitive, or motor problems. Severity of epilepsy was measured using the Global Assessment of Severity of Epilepsy (GASE), a validated single item 7-point scale shown to have moderate/strong correlations with several key clinical aspects of epilepsy [22,23]. In this report, GASE scores

range from 1 (“extremely severe”) to 7 (“not at all severe”). Presence of comorbidities at baseline was determined by physician report to three questions asking, “Does the patient have behavioural/cognitive/ motor problems”.

4.2.2.3 Parent and Family Characteristics

Parents reported on their age, sex, educational attainment, employment status, whether they live with a partner, and household income. Parents also completed a standardized measure of depressive symptoms and three standardized scales of family environment. Depressive symptoms were measured using the 20-item Center for Epidemiological Studies Depression Scale (CES-D) [24,25]. The CES-D uses a 4-point Likert scale, with scores ranging from 0 to 60 and higher scores indicative of greater depressive symptoms; internal consistency was $\alpha = 0.91$. Family demands were measured using the 71-item Family Inventory of Life Events and Changes (FILE) [26]. The FILE uses yes/no questions to evaluate the accumulation of normal and non-normal life events and changes in life events in the previous year. Scores range from 0 to 71, with higher scores indicative of greater demands; internal consistency was $\alpha = 0.83$. Family functioning was measured using the 5-item Family Adaptability, Partnership, Growth, Affection and Resolve (Family APGAR) [27]. The APGAR uses a 5-point Likert scale, with a total score ranging from 0 to 20 and higher scores indicative of greater satisfaction with family relationships; internal consistency was $\alpha = 0.87$. Lastly, level of family resources was measured using the Family Inventory of Resources for Management (FIRM; specifically, the family mastery and health subscale, and the extended family social support subscale) [26]. The 24 items in these subscales use a 4-point Likert scale with the total score ranging from 0 to 72. Higher scores indicate a more supportive, organized family environment with few disruptions in daily

routines and interactions, and greater extended family social support; internal consistency was α= 0.89.

4.2.3 Data Analysis

Analyses were conducted using SAS 9.4 (SAS Institute Inc. Cary, NC, USA). Mean and standard deviation (SD) were used to describe continuous variables, and proportions and percentages were used to describe categorical variables. To assess attrition bias, baseline characteristics of families that completed the 10-year follow-up to were compared with those who did not using univariable logistic regressions.

Distinct subgroups of children following a similar HRQOL trajectory over time were identified using latent class growth models (LCGM) with the Proc Traj macro [28]. The number of trajectory groups was guided by *a priori* expectations, overall model fit as assessed by the Bayesian Information Criterion (BIC), posterior probability, odds of correct classification, and proportion of individuals in each group [29]. Models with a different number of groups were compared using an estimate of the log Bayes Factor, which is approximately equal to two times the difference in the BIC values for the two models being compared; values ranging from 0 to 2 are interpreted as weak evidence for the more complex model (the model with the additional group), values ranging from 2 to 6 are interpreted as moderate evidence, values ranging from 6 to 10 are interpreted as strong evidence, and values greater than 10 are interpreted as very strong evidence for the more complex model [28]. Cubic trajectories were first specified for one group then additional groups were added until the model worsened [28]. Next, non-significant cubic or quadratic terms were removed to ensure model parsimony [31]. Results were consistent when a different set of start values were used. A probability of belonging to each group is assigned to each participant, and the participant is assigned to the group based on the highest probability

value. A censored normal model and an extension for LCGM to account for non-random attrition were used [32]. The extension for non-random attrition allows for the joint estimation of HRQOL trajectories and probability of dropping out; therefore, attrition was also used to inform the probability of group membership. The extension uses a logistic model of dropout probability included for each time point, and does not assume (as typically assumed with LCGM) that the probability of group membership and attrition are independent [32].

Once the groups were finalized, baseline child, parent, and family characteristics of the children in each trajectory group were compared. Analysis of variance and post hoc Tukey correction was used for continuous variables, and chi-square or Fishers' exact test was used for categorical data. Multinomial logistic regression was used to identify independent factors associated with each trajectory group. Only variables significant at $p < 0.20$ in the bivariate comparisons were included in a multivariable model [33]. Listwise deletion was used for missing data, as only 6% of the sample (n=23) were missing data on the variables of interest. The GASE and household income (each with ≥6 categories) were treated as continuous variables to obtain a more parsimonious model (results were similar when treated as categorical variables). Given that each comorbidity (cognitive, behavioral, and motor) was associated with the trajectory group, and given the overlap in comorbidities and sample size, having 'at least one comorbidity' was entered in the multivariable model. As a sensitivity analyses, the multivariable model was repeated after replacing 'have at least one comorbidity' with each type of comorbidity (cognitive, behavioral, and motor).

Lastly, we estimated the proportion of children with clinically significant changes in HRQOL in the long-term. In the absence of established thresholds for clinical significance, we utilized distribution-based methods focusing on the standard error of measurement (SEM) [34,35]. SEM was calculated from the baseline HRQOL assessment as: SEM = (SD) x √(1 –

[Cronbach's alpha]). To provide a conservative estimate, SEM was used to calculate the minimal detectable change (MDC) at alpha = 0.05 – the minimal magnitude of change required to be 95% confident that the observed change is a true change and not measurement error; MDC was calculated as (1.96) x (SEM) x √(2) [34,35].

4.3 Results

Families of 367 children completed HRQOL questionnaires and were included in this study. Table 4-1 presents a summary of the child, parent, and family characteristics. On average, children were 7.9 years of age at the time of diagnosis (standard deviation [SD]: 2.3, range: 3.8 to 12.6), and 17.9 years at the last follow-up (SD 2.6, range: 12.9 to 23.9). At the time of diagnosis, 61% had focal seizures, 26% had a cognitive, behavioral, and/or motor comorbidity, and the majority had "somewhat severe" (23%), or "a little severe" (35%) epilepsy, as indicated on the GASE. A detailed description of epilepsy/syndrome classification is presented in Table 4-2. At the 10-year follow-up, 85% had been seizure-free for the past year, and 66% had been seizure-free for the past 5 years. In addition, the majority (70%) had not received any epilepsy-related care from a doctor in the past year; an implication of this fact is unavailability of physician reports (e.g. on severity of epilepsy) at the 10-year follow-up.

Of the initial sample, 154 families participated in the sixth and final follow-up approximately 10 years after their child's diagnosis of epilepsy. It is important to note however, that the trajectory analysis utilises data from the full sample of 367 and accounts for any non-random loss to follow-up [32]. In addition, given that we focused on evaluating children's characteristics at the time of their diagnosis as potential as predictors of HRQOL, data from the full initial sample are included in these analyses. Nonetheless, we compared the baseline characteristics of children whose families did and did not complete the 10-year follow-up; results

are presented in Table 4-3. The HRQOL of children whose families completed the 10-year follow-up was similar at the time of diagnosis to those whose families did not (mean difference: 1.87, SD: 14.3, p = .23). Children in those families that did not complete the 10-year follow-up were more likely, at the time of diagnosis, to have cognitive problems, the participating parent was less likely to be living with their partner and reported more depressive symptoms and a poorer family environment (i.e. poorer household income, and family resources, demands and functioning).

4.3.1 Trajectories of health-related quality of life

The mean difference between baseline and 10-year follow-up HRQOL scores was an improvement of 6.8 points (95% CI 4.6 to 9.0; t_{149}=6.06, p<.0001), as indicated by a paired-samples t-test. Sample size, mean, and standard deviation of QOLCE-55 scores at each time point are presented in Table 4-4. Latent class growth modeling suggested that the data were best modeled as four subgroups of children with unique HRQOL trajectories (Table 4-5). Figure 4-1 presents the trajectories for each group and Figure 4-2 additionally shows the trajectory of each participant. Tables 4-6 and 4-7 provide the details of the model fit and scores at each time point, respectively. The first group, labeled *'Low-stable*' was composed of 11% of the sample who had relatively low HRQOL scores at the time of diagnosis and no significant change in scores over the follow-up. The second group, *'Intermediate-stable'* was composed of 18% of the sample who had intermediate scores at the time of diagnosis that remained relatively stable over the follow-up. The remaining two groups, composed of 71% of the sample, showed cubic trajectories with intermediate or high HRQOL at the time of diagnosis, initial improvements over the first two years, and a plateau over the long-term.

4.3.2 Factors Associated with Each Trajectory

Table 4-8 summarizes the child, parent, and family characteristics at the time of diagnosis of participants in each trajectory group, and Table 4-2 presents a more detailed account of the epilepsy/syndrome classification for each group. At the time of diagnosis, children with less severe epilepsy and without comorbidities, those with parents who had higher education and fewer depressive symptoms, and those with a better family environment (household income and family resources, demands, and functioning) were more likely to have a better long-term HRQOL trajectory. Given that each comorbidity (cognitive, behavioral, and motor) was associated with the trajectory group, having 'at least one comorbidity' was entered in the multivariable model, though results were similar when each comorbidity was entered individually (see below). Overall, the multivariable model showed that greater epilepsy severity, presence of comorbidities, and poorer satisfaction with family relationships at the time of diagnosis were significantly associated with poorer long-term HRQOL trajectories (Table 4-9). Greater family demands and poorer family mastery and less extended family support at the time of diagnosis were also associated with poorer long-term HRQOL trajectories, though not consistently.

As a sensitivity analyses, the multivariable model was repeated after replacing 'have at least one comorbidity' with each type of comorbidity (cognitive, behavioral, and motor). Results with respect to other variables in the model remained similar. With respect to the type of comorbidity, each was significantly associated with HRQOL trajectories, with cognitive problems showing the strongest association (Wald chi- square 38.11, *p* of overall effect <.0001), followed by behavioral (Wald chi- square: 20.47, *p* of overall effect <.0001) and motor problems (Wald chi-square 8.29, *p* of overall effect =.040). The Wald chi-square for 'at least one comorbidity' in the original model was 44.93, *p* of overall effect <.0001.

4.3.3 Individual Change

To estimate the proportion of children with a meaningful change in HRQOL, we calculated the minimal detectable change for overall HRQOL to be 8.16 points on the QOLCE-55. Among the 150 children with scores available both at baseline and 10-year follow-up, 43% showed an improvement and 13% showed a deterioration. Figure 4-3 presents the proportion of children with improved and deteriorated scores for each trajectory group. The more favorable trajectories (groups 3 and 4) had a larger proportion of children with improved scores, relative to the less favorable trajectories (groups 1 and 2).

4.4 Discussion

To our knowledge, this is the first study to prospectively evaluate, from the time of diagnosis, any aspect of long-term well-being of individuals with childhood-onset epilepsy. The results are novel in showing that changes in HRQOL observed over the first two years after diagnosis remain stable and are sustained over the long-term. Additionally, the results show, for the first time, that individual and family-level characteristics (epilepsy severity, child comorbidities and family environment at diagnosis) that predicted short-term HRQOL have longer term prognostic power and continue to predict long-term HRQOL trajectories. These results are important in identifying early in the course of epilepsy those children and families who are more likely to continue to experience problems in the long-term. Importantly, given that changes in HRQOL observed in the initial two years are sustained over the long-term, the initial period after diagnosis may be critical in determining how the children and families cope and may also set the stage for long-term outcomes, in which case, early intervention would be essential.

We found that one-third of children maintained a relatively poor level of HRQOL over the long-term, with the remainder showing initial improvements over the first two years that were sustained over the long-term. The proportion of children with poorer HRQOL trajectories may be underestimated, as discussed below. Results were heterogenous at the individual level as well, with 43% of children showing meaningful improvements and13% showing meaningful deteriorations. Initial improvements following diagnosis are not surprising and may occur as seizure control improves and the individual and family learn to cope with the daily limitations and accept the diagnosis, with help from their support system. Of course, it would be interesting to determine whether the level of improved and plateaued HRQOL observed at long-term follow-up is similar to the level of HRQOL prior to the diagnosis of epilepsy, if it were feasible in the future to design the type of study necessary to obtain this information from the phase prior to diagnosis.

Children with more severe epilepsy, with comorbidities (cognitive, behavioral and/or motor), and with a poorer family environment (specifically, lower satisfaction with family relationships, poorer family mastery, and greater family demands) at the time of epilepsy diagnosis were more likely to have poorer long-term HRQOL trajectories. These findings align with our group's previous report of the two-year trajectories for this patient group [6-8] and other studies of HRQOL trajectories 24 to 28 months post-diagnosis [9-11]. Epilepsy/syndrome classification was not associated with HRQOL trajectories, which aligns with the extant literature showing that epilepsy characteristics are not associated with HRQOL[15-17]. Notably, as the identified clinical factors remain largely unmodifiable, the impact of family environment is highlighted as a potential target for future interventions. We found that AYAs who had achieved seizure control at last follow-up were more likely to have a more favorable HRQOL trajectory, which is consistent with studies that have cross-sectionally evaluated HRQOL of

young adults with a history of childhood-onset epilepsy [12-14] or pediatric epilepsy surgery[36-39]. These studies have also identified that psychiatric disorders – particularly internalizing disorders – are strongly associated with HRQOL, perhaps more so than seizure control [12,13,38]. Other research has further shown that parent and family environment may have a greater impact on children's HRQOL and overall well-being, relative to epilepsy-specific factors [40,41]. Therefore, involving families in interventions and understanding the impact of epilepsy on the family and parents is important for the well-being of children with epilepsy and their family. Interventions targeting the family as a unit are warranted, and healthcare providers should be aware of the interrelationships among epilepsy, family environment, and the children's health and well-being [42]. These recommendations echo those proposed previously when we reported on the two-year HRQOL trajectories of this patient group [6,7]. Furthermore, the importance of family environment and these recommendations would not be limited to children with epilepsy, and are applicable to other chronic conditions.

Findings from the current study should be considered in the context of its limitations. First, the identified trajectories represent an approximation of a more complex reality and not necessarily distinct entities, as is the case with any LCGM analysis (Figure 4-2). Second, as with any long-term prospective study, attrition was inevitable because of loss of contact; we retained 72% and 42% of our sample by the 2-year and 10-year follow-up, respectively. Other studies that have evaluated the long-term HRQOL of childhood-onset epilepsy have similarly retained 37% [14] and 45% [12,13] of their sample. Notably, our study has a distinct advantage over past cross-sectional studies because we retained 100% of our sample in analyses; latent class growth curve modelling is a likelihood-based technique that utilizes data from the full sample (missing values are predicted based on those in the study and the characteristics of those who dropped out) and our evaluation of predictors of HRQOL trajectories utilized data from baseline which was

available for all participants. We also used an extension of latent class growth curve modeling that accounts for any non-random attrition by explicitly modeling the probability of dropping out and does not assume that the probability of group membership and attrition are independent[32]. Our study is also unique because we could identify the characteristics of participants lost to follow-up and estimate the impact of attrition on study results. We found that children lost to follow-up were more likely to have cognitive problems, and the participating parent was less likely to be living with their partner, reported more depressive symptoms, and reported a poorer family environment (i.e. poorer household income, and family resources, demands and functioning). These differences suggest that our results may underestimate the proportion of children with poorer HRQOL trajectories, and that results may not be generalizable to families facing greater adversities at the time of epilepsy diagnosis. However, with respect to HRQOL, age, sex, epilepsy/syndrome classification, epilepsy severity, and parent education employment, and living arrangement at the time of diagnosis, AYAs who did not complete the 10-year follow-up were similar to those who did complete the study at the time of diagnosis.

Third, children included in our cohort were also diagnosed with epilepsy between the ages of 4 and 12 years, and the results may not be generalizable to children diagnosed with epilepsy in early life, which is often associated with a more severe etiology. Children with progressive or degenerative neurological disorders were excluded from our cohort.

Fourth, an established threshold of a minimal clinically important difference was not available for the QOLCE as a measure of HRQOL. To deal with this limitation, we calculated minimal detectable change. A review by Norman et al. [43] has previously shown that estimates of a threshold of important change are consistently close to approximately one half of the standard deviation of baseline HRQOL. The identified threshold in this study is consistent with this estimate, finding that the identified threshold was 0.57 times of the standard deviation.

Nonetheless, it will be important for future studies to identify the minimal clinically important difference for the QOLCE.

Lastly, we evaluated children's and AYA's HRQOL as measured by a validated parent-reported measure (the QOLCE-55), and understand that self and parent reports may differ[44,45]. We were unable to obtain self-reported HRQOL across the stages of developmental from childhood to emerging adulthood given the lack of consistent and age appropriate self-reported HRQOL measures for children with epilepsy in the age range of this cohort [21]. Though our results are valid from the parents' perspective, it will be important for future studies to prospectively evaluate self-reported HRQOL trajectories over the long-term. In contrast to parents' reports, self-reports may be more optimistic given that parents report poorer HRQOL for their children compared with children's self-reports [44,45].

Overall, this study delineated the long-term trajectory of children's HRQOL after an epilepsy diagnosis, and identified the child, parent, and family characteristics at the time of diagnosis that continue to have a persistent effect in the long-term. The results are novel in showing that HRQOL improves for the majority of children in the first two years after diagnosis, and that these improvements are sustained over the long-term. There may be a critical period early in the course of the disorder during which interventions may be most effective. Family environment may be an optimal target for interventions, as it was the only modifiable factor independently associated with long-term HRQOL trajectories. These results are important in identifying prognosis beyond seizure control, and to allow for the identification of groups at risk of persistent problems over the long-term who may benefit from early interventions targeting children and their family.

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Figure 4-1. Children's health-related quality of life over the first 10 years after their diagnosis of epilepsy. Band around each trajectory represents the 95% confidence interval.

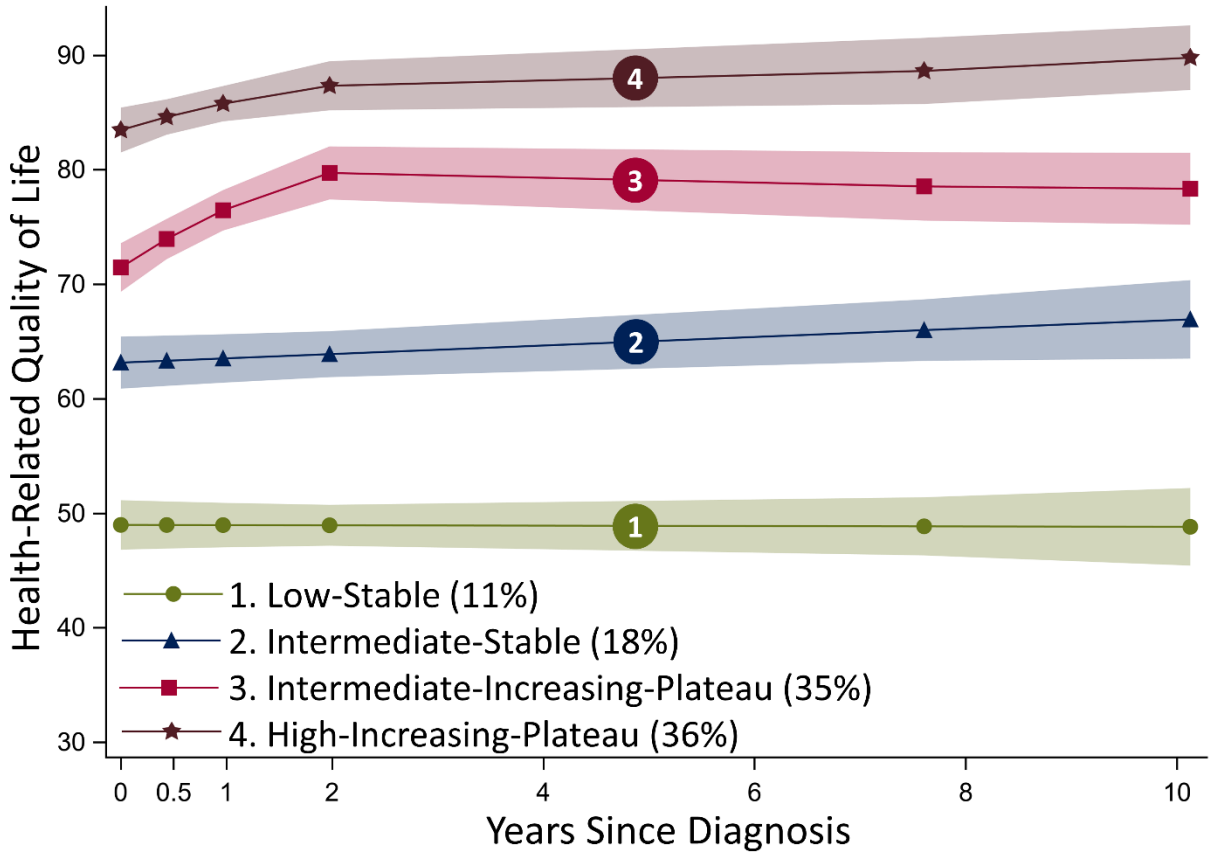
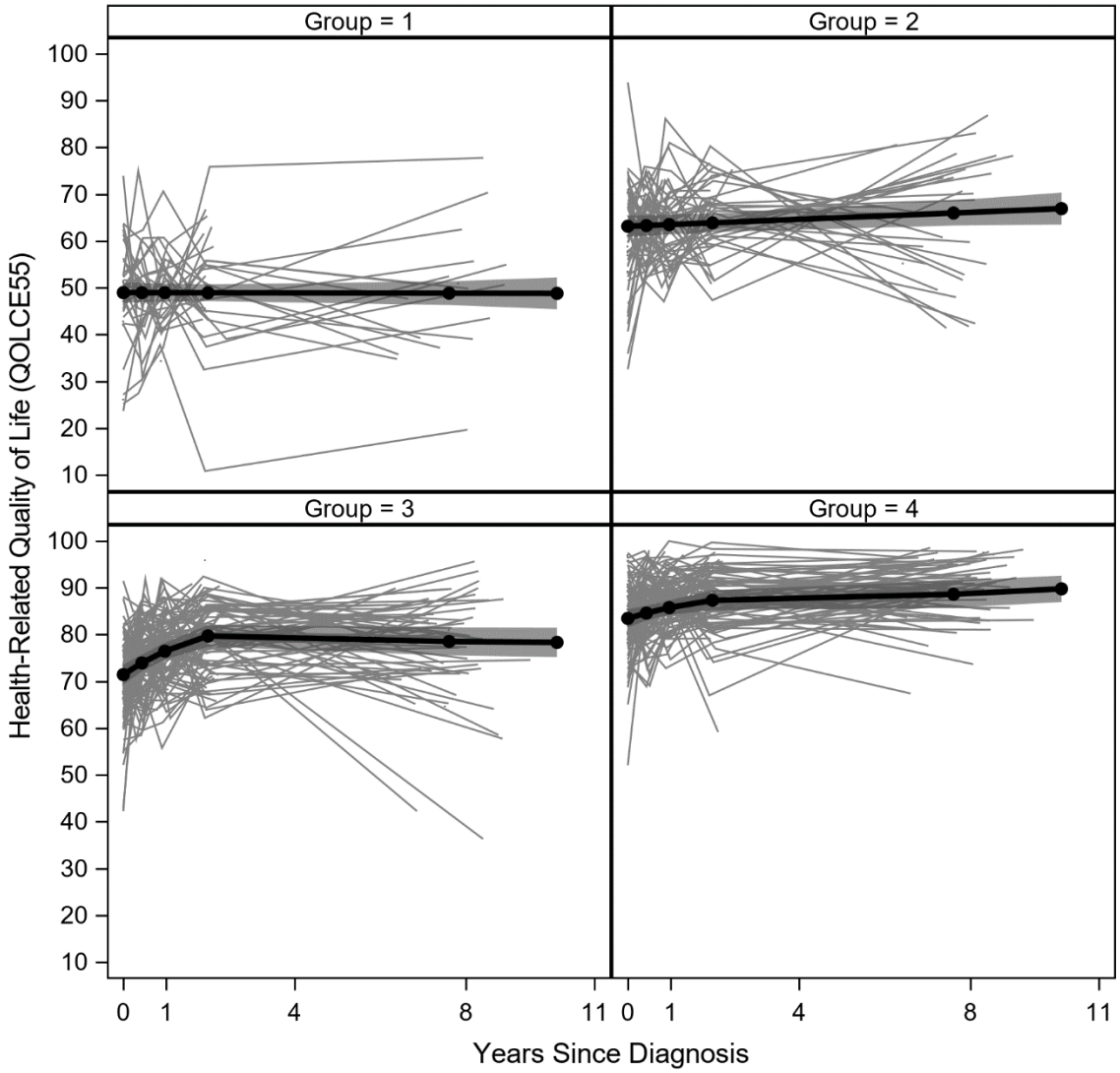


Figure 4-2. Trajectories for children's health-related quality of life during the first 10 years after the diagnosis of epilepsy.



Note: Thick solid lines and band depict predicted trajectories and 95% confidence interval of the entire group. Light lines depict the observed trajectory for each individual.

Figure 4-3. Proportion of children who showed improved and declined health-related quality of life scores at the 10-year follow-up, relative to baseline.

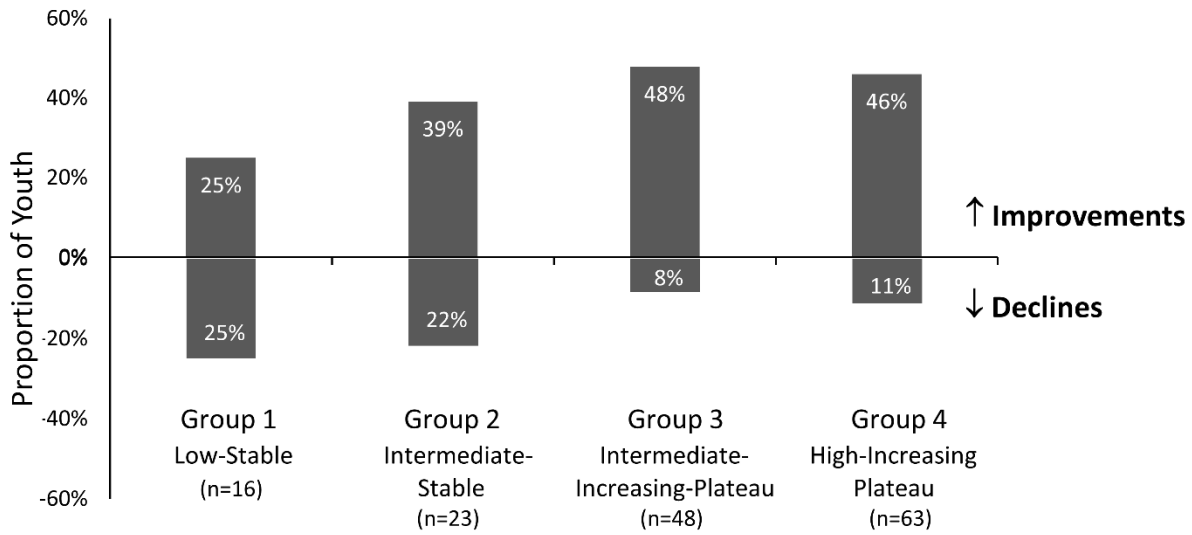


Table 4-1. Child, parent, and family characteristics at diagnosis (n=367) and at the 10-year follow-up (n=154).

Characteristics	At Diagnosis Mean (SD) or n (%)	10-Year Follow-up Mean (SD) or n (%)
Child		
Sex, # female	178 (49%)	68 (44%)
Age, years	7.9 (2.3)	17.9 (2.6)
Seizure classification [a, 5]		
Focal seizures	219 (61%)	–
Generalized seizures	143 (39%)	–
Epilepsy severity, GASE [a, 4]	5.4 (1.2)	–
Seizure free >1 year [5]	–	127 (85%)
Seizure free >5 years [5]	–	99 (66%)
Comorbidities [a]		
Cognitive	68 (19%)	–
Behavioral	51 (14%)	–
Motor	23 (6%)	–
At least one of the above	96 (26%)	–
Ever diagnosed with:		
Cognitive problems	–	60 (39%)
Behavioral problems	–	33 (21%)
Emotional problems	–	40 (26%)
Autism spectrum disorder	–	12 (8%)
At least one of the above		81 (53%)
Parent		
Sex, # female	342 (93%)	143 (93%)
Age, years [1]	38.1 (6.1)	48.9 (5.3)
College/university education	198 (54%)	104 (68%)
Works full or part time [3]	244 (67%)	119 (78%)
Living with partner	321 (87%)	135 (88%)
Depressive symptoms, CES-D [3]	14.2 (10.3)	9.3 (8.9)
Family		
Annual Household Income [10]		
< $20,000	27 (8%)	2 (1%)
$20,000 - $39,999	50 (14%)	15 (10%)
$40,000 - $59,999	77 (22%)	13 (9%)
$60,000 - $79,999	69 (19%)	19 (13%)
$80,000 - $99,999	50 (14%)	17 (12%)
$100,000 - $149,999	84 (23%)	33 (23%)
≥ $150,000		47 (32%)
Resources, FIRM [5]	50.3 (10.9)	52.6 (11.5)
Demands, FILE [4]	9.4 (6.3)	8.0 (5.7)
Functioning, APGAR [1]	13.9 (3.7)	15.0 (3.9)

Superscript numbers indicate the number of children with missing/unknown data at diagnosis.
[a] Data reported by children's neurologist; not available at last follow-up because the majority of adolescents and young adults had not received any epilepsy-related care from a physician in the 12 months prior to last follow-up. All other data is reported by parents.

Table 4-2. Seizure/syndrome classification at the time of diagnosis.

	Complete Cohort (n=367)	Group 1 Low-Stable (n = 41)	Group 2 Intermediate - Stable (n = 67)	Group 3 Intermediate - Increasing (n = 127)	Group 4 High-Increasing (n = 132)
Generalized	45 (12%)	8 (20%)	10 (15%)	13 (10%)	14 (11%)
Absence	97 (26%)	8 (20%)	15 (22%)	38 (30%)	36 (27%)
Focal	99 (27%)	13 (32%)	21 (31%)	35 (28%)	30 (23%)
BECRS	45 (12%)	1 (2%)	5 (7%)	18 (14%)	21 (16%)
Focal to bilateral tonic-clonic	44 (12%)	7 (17%)	10 (15%)	12 (9%)	15 (11%)
BECRS + focal to bilateral tonic-clonic	29 (8%)	2 (5%)	5 (7%)	9 (7%)	13 (10%)
Undetermined	8 (2%)	2 (5%)	1 (1%)	2 (2%)	3 (2%)

BECRS: Benign epilepsy of childhood with rolandic spikes.
Note: At the two-year follow-up, neurologist reported the same epilepsy / syndrome type among 84% of children

Table 4-3. Baseline characteristics of participants who completed (n=154) the 10-year follow-up compared to those who did not (n=213).

Baseline characteristics	Completed 10-year follow-up Mean (SD) or n (%)	Did not complete 10-year follow-up Mean (SD) or n (%)	Odds Ratio (95% CI) [a]
Child			
Health-related quality of life, QOLCE	72.3 (15.4)	70.4 (13.3)	0.99 (0.98, 1.01)
Sex, # female	68 (44%)	110 (52%)	1.35 (0.89, 2.05)
Age, years	7.8 (2.4)	8.0 (2.3)	1.04 (0.95, 1.13)
Focal seizures (ref=generalized) [b]	94 (61%)	125 (60%)	0.93 (0.61, 1.43)
Epilepsy severity, GASE [b]	5.5 (1.2)	5.3 (1.2)	0.91 (0.77, 1.09)
Comorbidities [b]			
Cognitive	15 (10%)	53 (25%)	3.07 (1.66, 5.69)
Behavioral	19 (12%)	32 (15%)	1.26 (0.68, 2.31)
Motor	7 (5%)	16 (8%)	1.71 (0.68, 4.25)
At least one of the above	28 (18%)	68 (32%)	2.11 (1.28, 3.48)
Parent			
Sex, # female	144 (94%)	198 (93%)	0.92 (0.40, 2.10)
Age, years	38.8 (5.3)	37.6 (6.6)	0.97 (0.94, 1.00)
Living with partner	142 (92%)	179 (84%)	0.45 (0.22, 0.89)
Works full or part time	105 (68%)	139 (66%)	0.91 (0.59, 1.42)
College/university education	90 (58%)	108 (51%)	0.73 (0.48, 1.11)
Depressive symptoms, CESD	11.9 (9.9)	15.8 (10.2)	1.04 (1.02, 1.07)
Family			
Annual Household Income			0.78 (0.68, 0.90)
< $20,000	5 (3%)	22 (11%)	
$20,000 - $39,999	14 (9%)	36 (18%)	
$40,000 - $59,999	35 (23%)	42 (20%)	
$60,000 - $79,999	27 (18%)	42 (20%)	
$80,000 - $99,999	28 (18%)	22 (11%)	
≥$100,000	43 (28%)	41 (20%)	
Resources, FIRM	52.9 (11.0)	48.4 (10.4)	0.96 (0.94, 0.98)
Demands, FILE	8.4 (5.9)	10.2 (6.5)	1.05 (1.01, 1.09)
Functioning, APGAR	14.8 (3.8)	13.3 (3.6)	0.89 (0.84, 0.95)

[a] Odds ratio (95% confidence interval) of dropping out of the study.

[b] Data presented are parent reported, except for those denoted by superscript [b] which are physician reported.

Table 4-4. Sample size, mean, and standard deviation (SD) of QOLCE-55 scores at each time point.

	All Participants		Participants with baseline and follow-up scores *	
	n	Mean (SD)	n	Mean (SD)
Diagnosis	350	71.2 (14.3)	150	72.3 (15.4)
6-month follow-up	315	74.3 (13.5)	150	75.1 (14.3)
1-year follow-up	287	75.4 (13.9)	150	76.5 (14.3)
2-year follow-up	265	76.8 (14.5)	150	77.2 (15.2)
8-year follow-up	178	77.4 (16.6)	150	77.0 (17.4)
10-year follow-up	154	78.6 (16.3)	150	79.1 (15.5)

* Given the inevitable attrition of long-term follow-up, we also evaluated HRQOL scores for the sub-sample of children with HRQOL scores at baseline and the 10-year follow-up.

Table 4-5. Model fit indices when different numbers of groups were specified.

Number of groups	BIC	Logged Bayes factor [a]	Overall Posterior Probability (Min, Max)	Proportion of patients in each group
2	-6475.88	-	0.955 (0.937, 0.961)	29%, 71%
3	-6391.65	168.46	0.904 (0.870, 0.924)	16%, 35%, 49%
4	-6389.04	5.22	0.841 (0.787, 0.908)	11%, 19%, 34%, 36%
5	-6397.77	-17.46	0.827 (0.757, 0.886)	12%, 15%, 19%, 42% 12%
6	-6522.51	-249.48	0.798 (0.742, 0.921)	7%, 10%, 11%, 9%, 30%, 32%

[a] Calculated as $2*(BIC_{[complex]} - BIC_{[null]})$; where the more complex model is the one with the greater number of groups. Values ranging from 0 to 2 are interpreted as weak evidence for the more complex model, values ranging from 2 to 6 are interpreted as moderate evidence, values ranging from 6 to 10 are interpreted as strong evidence, and values greater than 10 are interpreted as very strong evidence for the more complex model [28].
BIC: Bayesian information criterion

Table 4-6. Estimates of health-related quality of life trajectory parameters.

Group	Sample size	% Sample	Posterior Probability [a]	OCC [b]	Parameter	β (Standard Error)	p-value
1. Low-Stable	41	11.2%	.889	64.9	Intercept	48.98 (1.10)	<.0001
					Linear	-0.02 (0.21)	.94
2. Intermediate-Stable	67	18.3%	.808	17.7	Intercept	63.16 (1.16)	<.0001
					Linear	0.37 (0.20)	.059
3. Intermediate-Increasing-Plateau	127	34.6%	.780	7.1	Intercept	71.46 (1.07)	<.0001
					Linear	6.22 (1.10)	<.0001
					Quadratic	-1.14 (0.25)	<.0001
					Cubic	0.06 (0.02)	.0002
4. High-Increasing-Plateau	132	36.0%	.894	14.6	Intercept	83.55 (0.83)	<.0001
					Linear	2.92 (0.93)	.0017
					Quadratic	-0.49 (0.21)	.021
					Cubic	0.03 (0.01)	.045

[a] Values greater than 0.70 are deemed acceptable and indicative of high assignment accuracy
[b] OCC: Odds of Correct Classification, values greater than 5.0 suggest that the model has high assignment accuracy

Table 4-7. Estimated mean health-related quality of life scores (95% confidence interval) at each time point for each trajectory group.

Group	At Diagnosis	6 Months Follow-up	1 Year Follow-up	2 Years Follow-up	8 Years Follow-up	10 Years Follow-up
Time [a]	0.00 (0.00)	0.43 (0.09)	0.97 (0.12)	1.98 (0.12)	7.61 (0.81)	10.13 (0.82)
1. Low-Stable	49.0 (46.8, 51.1)	49.0 (46.9, 51)	49.0 (47.0, 50.9)	48.9 (47.2, 50.7)	48.9 (46.3, 51.4)	48.8 (45.4, 52.2)
2. Intermediate-Stable	63.2 (60.9, 65.4)	63.3 (61.1, 65.5)	63.5 (61.4, 65.6)	63.9 (61.9, 65.9)	66.0 (63.3, 68.7)	66.9 (63.5, 70.4)
3. Intermediate-Increasing-Plateau	71.5 (69.3, 73.6)	74.0 (72.2, 75.7)	76.5 (74.7, 78.2)	79.7 (77.4, 82.0)	78.5 (75.6, 81.5)	78.3 (75.2, 81.5)
4. High-Increasing-Plateau	83.5 (81.5, 85.4)	84.6 (83.1, 86.2)	85.8 (84.2, 87.3)	87.3 (85.2, 89.5)	88.6 (85.7, 91.5)	89.8 (87.0, 92.6)

[a] Mean time (in years) since children's epilepsy diagnosis (standard deviation)

Table 4-8. Baseline characteristics of children in each trajectory group.

Baseline Characteristics	Group 1 Low-Stable (n = 41)	Group 2 Intermediate -Stable (n = 67)	Group 3 Intermediate -Increasing (n = 127)	Group 4 High-Increasing (n = 132)	F/χ2 (p-value)	Contrasts [a]
Child						
Sex, # female	22 (54%)	23 (34%)	70 (55%)	63 (48%)	8.1 (.044)	–
Age, years	7.9 (2.5)	7.7 (2.3)	7.9 (2.3)	8.1 (2.4)	0.5 (.69)	
Focal seizures	23 (60%)	42 (63%)	75 (60%)	79 (61%)	0.2 (.97)	
Epilepsy severity, GASE	5.0 (1.4)	5.0 (1.3)	5.6 (1.0)	5.5 (1.2)	5.2 (.0017)	3 > 1,2
Comorbidities						
Cognitive	22 (54%)	25 (37%)	18 (14%)	3 (2%)	73.9 (<.0001)	1,2>3,4; 3>4
Behavioral	16 (39%)	17 (25%)	13 (10%)	5 (4%)	41.7 (<.0001)	1,2>3,4; 3>4
Motor	6 (15%)	8 (12%)	8 (6%)	1 (1%)	(.0004) [b]	1,2,3>4
At least one of the above	26 (63%)	33 (49%)	30 (24%)	7 (5%)	78.1 (<.0001)	1,2>3,4; 3>4
Seizure free >1-year [c]	9 (56%)	22 (85%)	45 (85%)	69 (95%)	(.0016) [b]	3,4>1
Seizure free >5-years [c]	2 (13%)	15 (58%)	34 (65%)	63 (86%)	35.4 (<.0001)	2,3>1; 4>1,2,3
Parent						
Sex, # female	40 (98%)	64 (96%)	119 (94%)	119 (90%)	(.36) [b]	
Age, years	38.1 (7.5)	37.6 (5.9)	37.6 (6.0)	38.9 (5.8)	1.31 (.27)	
Living with partner	35 (85%)	56 (84%)	108 (85%)	122 (92%)	4.7 (.19)	
Works full or part time	28 (68%)	41 (62%)	82 (65%)	93 (71%)	1.9 (.59)	
College/university	13 (32%)	29 (43%)	73 (57%)	83 (63%)	16.1 (.0011)	3>1; 4>2,1
Depressive symptoms	20.1 (10.7)	17.5 (10.8)	14.0 (9.2)	10.8 (9.5)	12.7 (<.0001)	1>3; 1,2,3>4
Family						
Annual Household Income					4.6 (.004)	4 > 1
< $20,000	8 (20%)	8 (12%)	5 (4%)	6 (5%)		
$20,000 - $39,999	3 (8%)	10 (15%)	27 (22%)	10 (8%)		
$40,000 - $59,999	14 (35%)	12 (18%)	28 (23%)	23 (18%)		
$60,000 - $79,999	6 (15%)	10 (175)	18 (15%)	35 (27%)		
$80,000 - $99,999	6 (15%)	7 (11%)	16 (13%)	21 (16%)		
>$100,000	3 (8%)	18 (28%)	29 (24%)	34 (26%)		
Resources, FIRM	43.8 (12.3)	46.7 (10.2)	49.0 (9.8)	55.3 (9.7)	19.4 (<.0001)	4 > 3,2,1; 3>1
Demands, FILE	12.9 (7.4)	10.4 (5.3)	10.1 (6.9)	7.1 (5.0)	11.9 (<.0001)	1,2,3 > 4
Functioning, APGAR	11.8 (4.3)	12.8 (3.6)	14.0 (3.4)	15.1 (3.5)	11.7 (<.0001)	4 > 1,2; 3>1

Mean (Standard Deviation) or n (%) are presented.

[a] Denotes significant pairwise contrasts (at $p<.05$), e.g. 2,3>1 indicates that Group 2 and 3 are significantly larger (or have higher scores) than Group 1;

[b] p-value of Fisher's exact test;

[c] Provided as a descriptive statistic, is based on the data from the 10-year follow-up visit and therefore was not considered in multivariable regression; data available for 168 adolescents and young adults.

Table 4-9. Odds of belonging to each group trajectory relative to Group 4 (*High-Increasing-Plateau*).

Baseline Characteristics	*p*-value of overall effect	*1. Low-Stable* OR (95% CI)	*2. Intermediate-Stable* OR (95% CI)	*3. Intermediate-Increasing-Plateau* OR (95% CI)
Child				
Sex (ref=female)	.07	1.67 (0.66, 4.21)	0.60 (0.29, 1.22)	1.28 (0.74, 2.21)
Epilepsy severity, GASE	**.006**	**0.69 (0.48, 0.99)**	0.80 (0.61, 1.06)	1.19 (0.94, 1.51)
Any comorbidity	**<.0001**	**35.72 (11.35, 112.47)**	**13.42 (5.11, 35.21)**	**4.44 (1.78, 11.04)**
Parent				
Living with partner	.24	2.52 (0.53, 12.08)	0.77 (0.22, 2.64)	0.63 (0.23, 1.71)
College/university education	.19	0.43 (0.16, 1.14)	0.58 (0.28, 1.21)	1.00 (0.56, 1.79)
Depressive symptoms	.22	1.04 (0.99, 1.09)	1.04 (1.00, 1.08)	1.01 (0.97, 1.04)
Family				
Household Income	.61	0.83 (0.60, 1.15)	1.03 (0.8, 1.33)	0.97 (0.79, 1.19)
Resources, FIRM [d]	.12	0.98 (0.92, 1.03)	0.97 (0.92, 1.01)	**0.96 (0.92, 0.99)**
Demands, FILE [e]	.08	**1.10 (1.01, 1.19)**	1.04 (0.97, 1.12)	**1.07 (1.01, 1.13)**
Functioning, APGAR [f]	**.030**	**0.83 (0.72, 0.96)**	0.91 (0.81, 1.03)	1.00 (0.91, 1.11)

OR odds ratio; CI confidence interval. Bolded items highlight statistical significance.

[d] Higher scores are indicative of greater of more supportive, organized family environment with few disruptions in daily routines and interactions, and greater extended family social support

[e] Higher scores are indicative of greater family demands and stress

[f] Higher scores are indicative of greater satisfaction with family relationships

Chapter 5: Systematic review of quality of life in parents of children with epilepsy [1]

5.1. Introduction

Childhood-onset epilepsy extends beyond seizures, with children experiencing a wide range of cognitive, psychiatric, and behavioral comorbidities that often go under-recognized and untreated [1-3]. In addition, families of children with epilepsy (CWE) have been found to experience greater stress, poorer quality of parent-child relationships, lower parenting confidence, and more problems in family functioning, adaptation, and relationships, relative to other families [4]. Recent systematic reviews of parents of CWE report that up to 58% score in the clinical range for anxiety symptoms [5], and up to 50% of mothers are at risk for clinical depression [6]. Importantly, psychosocial factors, family environment, and parental well-being often have a greater impact on children's health-related quality of life (QOL), depression, anxiety, and behavioral problems than epilepsy-related factors [4-10]. This finding is echoed in other childhood chronic conditions, where the most important factors for adaptation and well-being are individual and family characteristics, rather than illness characteristics [11]. However, epilepsy-related characteristics remain important in understanding parental outcomes. The Caregiving Process Model adapted for CWE [12,13] aids in the conceptualization of the complex interplay between epilepsy, individual, and family characteristics, and ultimately the manifestation of parental outcomes, namely QOL. In this model, the first domain consists of child/clinical characteristics (e.g. illness severity, time since diagnosis, comorbidities), family environment (e.g. financial status, education, employment), parents' psychosocial factors (e.g. caregiver strain, stress response to children's illness), and the interactions between these factors.

[1] A version of this chapter has been published: Puka K, Tavares PT, Anderson KK, Ferro MA, Speechley KN (2018). A systematic review of quality of life in parents of children with epilepsy. Epilepsy & Behavior 82, 35-45. DOI: 10.1016/j.yebeh.2018.03.008

These factors impact the second domain, coping resources (e.g. self-efficacy, social support), followed by management behaviors (e.g. treatment plan management, lifestyle behaviors, interactions with healthcare providers), and ultimately lead to caregiver outcomes (e.g. QOL, physical symptoms, psychological symptoms, functional status).

Although the majority of past studies and systematic reviews have focused on symptoms of anxiety and depression in parents of CWE, little is known about their QOL. Health-related QOL is a multidimensional construct encompassing the individual's subjective perception of their physical health, psychological well-being, social functioning, and independence [14]. Although symptoms of depression and anxiety may impact health-related QOL, instruments developed to measure health-related QOL reflect individual perceptions of the influence of disease and treatment on function, and are not interchangeable with instruments that measure symptoms or impairments, such as measures of anxiety and depression [15,16]. Health-related QOL is an important construct in understanding how parents respond, adapt, and cope with the challenges of childhood-onset epilepsy and other stressors, as conceptualized by the Caregiving Process Model, and may provide targets for potential interventions. To date, there have been no reviews evaluating the QOL of parents of CWE.

The current study aimed to provide a succinct review of the literature evaluating the QOL of parents of children with epilepsy; an area of research that has been neglected and warrants further research. Specifically, the primary aim was to systematically review the literature to describe QOL for parents of children with childhood-onset epilepsy. Our secondary aims were to identify factors associated with parental QOL, and to evaluate the association between parents' QOL and their children's psychological well-being, namely QOL, depression and anxiety. We hypothesized that 1) parents of children with epilepsy will have poorer QOL relative to healthy controls, 2) that the most proximal factors to parental outcome, as outlined in the Caregiving

Process Model, would have the largest impact on parental QOL, and 3) parents' QOL will be strongly correlated with their children's psychological well-being.

5.2. Methods

5.2.1 Definition of Quality of Life

As mentioned, health-related QOL is a broad construct that encompasses many domains of life, including physical health, psychological well-being, social functioning, and independence. Health-related QOL is thought to be encompassed within the larger construct of QOL, which reflects individuals' perception of their position in life, within the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns [17]. In contrast, health-related QOL is focused on the impact of illness and treatments on a person's life, and does not pertain to aspects of life that cannot be influenced by healthcare intervention, such as environmental quality and political stability [18]. The current review was inclusive of studies evaluating health-related QOL specifically, or QOL more generally.

5.2.2 Search Strategy and Study Selection

We conducted a comprehensive search of MEDLINE (Ovid), EMBASE (Ovid), and PsycINFO on May 5, 2017, using a combination of subject headings and keywords relating to 1) quality of life, 2) epilepsy, and 3) parents. Specifically, we searched for (exp "Quality of Life"/ or quality of life) and (exp Epilepsy/ or epilepsy) and (exp Parents/ or parent* or mother or maternal or father or paternal), and restricted the search to studies in humans and published in English. There were no date restrictions. To ensure no records were omitted from the search strategy, reference lists of all included studies were manually searched (backward citation tracking), and Web of Science, Scopus, and Google Scholar were used to identify articles citing

these studies (forward citation tracking). In addition, alerts were set on Google Scholar to identify studies published after the search date using the terms: (quality of life) and (epilepsy) and (parent* or mother or maternal or father or paternal). This alert was discontinued on December 31, 2017.

Articles were included if they quantitatively reported on the QOL of parents (or guardians) of individuals with childhood-onset (<18 years of age) epilepsy. Review articles, case-studies, and conference abstracts were excluded; we contacted authors of abstracts of unpublished studies to determine whether the studies had been published subsequently in a peer-reviewed journal, though no eligible studies were identified using this method. Among the conference abstracts excluded, no information on parents' QOL was available to be extracted. All identified articles were screened by two independent reviewers (KP & TPT). First, title and abstracts were checked and studies reporting, or thought to potentially report, on the QOL of parents of individuals with childhood-onset epilepsy were retained; inter-rater reliability was $\kappa = 0.46$. Second, the full text of each article was checked and studies meeting inclusion criteria were retained; inter-rater reliability was $\kappa = 0.85$. Any disagreements between reviewers were discussed among the two reviewers and resolved by consensus.

5.2.3 Quality Check

All included studies were evaluated by two independent reviewers using a modified version of the Downs and Black Quality Index [19]. Items specific to intervention studies, such as randomization and blinding, were removed, reducing the Quality Index to 15 items. The modified index is presented on Table 5-1, and has been used by past systematic reviews on similar topics [6]. The Quality Index is composed of four subscales: reporting quality, external

validity, internal validity, and statistical power. Each checklist item was scored as 0 (no/unable to determine) or 1 (yes), where higher scores reflect higher methodologic quality.

5.2.4 Data Extraction and Synthesis

Data relevant to describing patient and parent characteristics, parental QOL, and factors associated with parental QOL were extracted by one reviewer (KP), and verified by a second independent reviewer (TPT). When methodological questions arose or if more detailed data were required, corresponding authors were contacted; of the 12 corresponding authors contacted, 7 responded, though the requested information was not always available. Although the Short-Form health survey (SF-36 or SF-12) was employed by eight studies to evaluate parental QOL, the available data, the heterogeneity in patient samples, and the subscales reported did not allow for a meta-analysis. Similarly, in evaluating factors associated with parental QOL, operationalization of the factors, analyses used, and data reported varied among studies which did not allow for a meta-analysis. Results of univariable and multivariable analyses were reported for each study. Results of univariable analyses were combined and presented for the factors that were examined in at least two studies. Similar methods have been utilized by prior systematic reviews and meta-analyses evaluating risk factors [20].

5.3. Results

5.3.1 Search results

PRISMA reporting guidelines were followed [21]. The search strategy identified 709 records, of which 62 underwent full-text screening, and 11 met the inclusion criteria (Figure 5-1). Forward citation tracking identified one additional article, and the automated alerts of studies

published after the search date identified three articles. Therefore, 15 articles were included in this systematic review [22-36].

Some articles reported on different aspects of the same study, utilizing the same parent sample. In these cases, we aimed to include as much information as possible from all articles, while avoiding data duplication. Articles reporting on the same parent sample were: 1) Moreira et al. [31] and Carona et al. [32], we primarily focused on the results of Moreira et al. [31], which presented parental QOL relative to a control group; 2) Mori et al. [27] and [28], we primarily focused on Mori et al. [27], which examined parents of CWE; 3) Reilly et al. [22] and [23], we presented results from both studies because they were conducted at different time points; and, 4) Soria et al. [35] and [36], we primarily focused on Soria et al. [35], which examined parents of CWE.

5.3.2 Study and participant characteristics

The included studies were published between 2009 and 2018. The characteristics of these studies are presented in Table 5-2. The majority were conducted in Europe [22,23,26,30,31,33-35] and others in North America [24], and Asia [25]; two recruited participants from multiple countries [27,29]. Of note, most studies recruited participants through outpatient hospital visits (77%), and were multicentred (69%). Three studies excluded patients with intellectual disability or other comorbidities [25,31,33], and three studies excluded patients with progressive neurodegenerative disorders [24-26]. Two other studies focused on patients with specific syndromes: Mori et al. [27] studied patients with CDKL5, a rare X-linked genetic disorder associated with epilepsy and severe developmental delays; and Gallop et al. [29] studied patients with Lennox-Gastaut Syndrome, a syndrome associated with seizures that are difficult to control and require life-long treatment and usually, but not always, accompanied by impaired intellectual

development. One study examined patients with moderate to severe developmental delay who were starting the ketogenetic diet [34]. Ten studies reported cross-sectional data on parents' QOL, and three evaluated parents' QOL at two time points; one reported parents' QOL at baseline and two years after epilepsy surgery [23], one reported baseline and after one year on the ketogenic diet [34], and another at baseline and five to seven months after a sleep monitoring intervention [30].

Child and parental characteristics are presented in Table 5-3. Of note, the included studies predominantly evaluated QOL in mothers, with only three studies reporting QOL in fathers [22,23,36] (two of these studies reported on the same parent group [22,23]). In addition, the majority of studies concentrated on children with active epilepsy, with only one reporting on long-term outcomes with the majority of patients seizure-free [24].

Table 5-4 presents a summary of the modified Downs and Black quality assessment. Reporting quality was good, with 9 of the 12 studies meeting 6 or 7 of 7 criteria. External and internal validity were good, with 10 out of 12 studies meeting 2 or 3 of 3 criteria for external validity, and 10 studies of 12 meeting 3 or 4 of the 4 criteria for internal validity. Only one study reported a sample size calculation. Study results were synthesized through a comprehensive narrative review and generally showed the same trend across studies. When differences in study findings were apparent, these are discussed and appear to be a result of differences in QOL measures and patient populations, as opposed to differences in study quality.

5.3.3 Parental QOL

Our first objective was to describe QOL in parents of children with childhood-onset epilepsy. A summary of results from each study is presented in Table 5-5, and Table 5-6 presents a summary of the QOL measures utilized. QOL was predominantly evaluated using the Short-

Form health survey (SF-36 or SF-12; evaluating HRQOL) [22-27,29,30]; other measures evaluated QOL using the WHOQOL-BREF [32], the EUROHIS-QOL-8 [31,33], a single item QOL measure [34], and the Parental QOL Difficulties Questionnaire [35]. The SF-36 and SF-12 generates eight subscales and two composite scales relating to mental health-related QOL and physical health-related QOL. Seven (out of eight) studies employing the SF-36 or SF-12 found that parents of CWE had poorer mental health-related QOL relative to population norms or control groups [22,23,25-27,29,30], and one study reported similar mental health-related QOL [24]. This latter study was unique in evaluating long-term outcomes (10 years after diagnosis) where the majority of children were seizure-free [24]. Six studies reported that parents of CWE had similar or marginally better physical health-related QOL relative to controls [22-24,26,27,29]; however, two studies reported poorer scores on some subscales relating to physical health-related QOL [22,23]. The two studies utilizing the EUROHIS-QOL-8 reported a similar overall QOL relative to controls [31,33].

Three studies compared the QOL of parents of CWE and parents of children with other chronic conditions. Moreira et al. [31] found that the QOL of parents of CWE was better relative to parents of children with obesity and similar to parents of children asthma, diabetes, and cerebral palsy. Soria et al. [36] found similar QOL among parents of CWE and children with brain tumours. Mori et al. [28] found that parents of CWE (those with CDKL5) had poor mental health-related QOL, and better- physical health-related QOL, relative to parents of children with Down syndrome and Rett syndrome.

5.3.4 Factors associated with parental QOL

Our second objective was to identify the factors associated with parental QOL. Few studies reported on the factors associated with parental QOL, often with different variables of

interest. Table 5-7 presents a summary of the factors evaluated by at least two studies and the bivariate relationship between each factor and parental QOL. Studies consistently found that better QOL in children [31,33], greater parental anxiety [22,25] and depressive symptoms [22,24,25], and lower socioeconomic status were associated with poorer parental QOL [24,25,27,33]. Although studies have predominantly focused on mothers (with few exceptions [22,23,36]), mothers of CWE were found to have lower QOL relative to fathers in three European studies [22,33,36], but no significant relationship was found in one Asian study [25]. Two studies found that seizure control was associated with better parental QOL [24,25], and two studies found no significant relationship [27,33]. Parents' education [24,25,27], and children's age [24,25,27,31,33], age of seizure onset [24,25], and number of antiepileptic drug [24,25] have not been associated with parental QOL. Inconsistent results have been reported in terms of family size, patients' sex, and parents' age and employment [24,25,27,33]. Table 5-5 presents a summary of multivariable and other study findings, and highlights the association between family environment and psychosocial factors with parents' QOL.

5.3.5 Parental QOL and their children's well-being

Our third objective was to evaluate the association between parents' QOL and their children's psychological well-being, namely QOL, depressive symptoms, and anxiety. Only two studies addressed this question, with bivariate analyses showing that better parental QOL was associated with better QOL in their children [31,33]. One of the studies evaluated this relationship in a multivariable model, finding no significant relationship when adjusting for child internalizing and externalizing problems [31].

5.4. Discussion

This review adds to the literature by providing a comprehensive evaluation of the QOL of parents of CWE relative to healthy controls and parents of children with other chronic conditions, and identifying key factors associated with parental QOL. This review also evaluated the association between the QOL of parents and their children, and identified a number of limitations in the literature evaluating parental QOL. Specifically, we found that parents of CWE had poorer QOL relative to healthy controls and population norms, but similar QOL to parents of children with other chronic conditions. Although clinical factors are a major stressor for poor QOL, the results of this review highlight the role of family environment and psychosocial factors in determining parents' QOL.

Our first objective was to describe the QOL of parents of CWE, finding that their QOL (particularly their mental health-related QOL) was poorer relative to healthy controls, and similar to parents of children with other chronic conditions or disabilities. Not surprisingly, greater child care needs have been associated with greater parental burden and poorer parental QOL in epilepsy and other chronic conditions, likely associated with symptoms of burnout and restricted social contacts and family interactions [26,37]. Consequently, children with the greatest needs may be cared for by parents with poor mental and physical health-related QOL. Two studies included in this review found that QOL in parents of CWE was similar to that of controls at the group level using the EUROHIS-QOL-8 scale [31,33]. Four studies utilizing the SF-36 or SF-12 reported better physical health-related QOL [23,24,27] in parents of CWE, though this result should be interpreted with caution. Researchers have expressed concern of artificially inflated physical health-related QOL scores among individuals with substantially lower mental health-related QOL, and vise-versa [38-42]. This concern originates from the orthogonal-factor analytic

model used to generate the mental and physical health-related QOL composite scores, which forces these scores to be uncorrelated.

Our secondary objective was to identify the factors associated with parental QOL. Child/clinical characteristics, family environment, and caregiver psychosocial factors were predominantly evaluated; the impact of coping resources and management behaviors (the second and third domain of the Caregiving Process Model) have received limited investigation. Family environment and psychosocial factors were found to be more robust determinants of parent QOL than child/clinical characteristics. Results were similar among the three studies that focused on children with more severe syndromes [27,29,34]. We found that parental QOL was consistently associated with, and often most impacted by, parental anxiety and depressive symptoms, and poorer socioeconomic status [22,24,25,33]. Seizure control was not consistently associated with parental QOL [24,25,27,33]. Patients' sex, age, age at seizure onset, use of antiepileptic drugs, and parents' age and education, were not associated with parental QOL. Mothers had poorer QOL relative to fathers [22,33,36], with similar results previously reported for symptoms of anxiety, depression and stress in epilepsy and other conditions [5,43]. However, it is important to note that this presents an area of future research, as the majority of studies on parental QOL (as well as anxiety, depression, and stress) are primarily focused on mothers. We cannot identify whether this result is specifically attributed to sex differences, or whether it is associated with being a primary caregiver. Though mothers are often the primary caregiver, epilepsy affects the entire family and the impact on fathers remains poorly understood [44-46].

The results of this systematic review, and research in other chronic conditions, highlight the integral role of family environment and psychosocial factors, which may mitigate the impact of the severity of childhood illness on parental psychological well-being, in line with the Caregiving Process Model [24,32,33,37,47]. However, these studies generally utilize simple

study designs evaluating cross-sectional results; only one study has utilized more complex design/analysis. Carona et al. [32] found that the impact of caregiver burden on the QOL of parents with CWE is indeed mediated by the parents' coping strategies. Similarly, among parents of children with other chronic conditions, the association between parental QOL and burden of care is diminished when controlling for social support, coping skills, financial burden, and whether the parents feel that they need more help in the household [37,48]. These results suggest that although the severity of the epilepsy and other disease-specific factors may be a major stressor for poorer QOL, family environment, psychosocial factors, coping resources, and management behaviors are important intermediaries in the manifestation of parental outcomes, and may be targeted for intervention. However, there is a need for more studies utilizing complex study designs and evaluating mediating and moderating effects between factors.

Our third objective was to evaluate the relationship between parental QOL and their child's psychological well-being, namely children's QOL, depression and anxiety symptoms. Only the association between parent and child QOL was evaluated by the included studies, showing significant correlations [31,33]. This aligns with past research showing that family environment and psychosocial factors are strongly associated with children's QOL and psychopathology [4-10].

A limitation of the literature evaluating QOL in parents of CWE is the cross-sectional nature of the studies. Though three studies evaluated parents at two time points [23,30,34], their aim was to evaluate an intervention. Only one study focused on patients with new-onset epilepsy, but aimed to evaluate the impact of a sleep monitoring intervention, without an evaluation of the impact of child factors, family environment and psychosocial factors on parental QOL. Consequently, a causal relationship cannot be determined for the strong correlations among parental QOL with coping, social support, family environment, and their child's QOL.

Furthermore, the natural course of parental QOL throughout their child's epilepsy management is unknown, and presents an area for future research; work with focus groups has shown that the needs and concerns of parents of CWE change over time [13]. In addition, almost all studies recruited patients through outpatient hospital clinics, limiting the generalizability of results to parents of children primarily seen by community physicians. The majority of studies relied on population-based norms in describing the QOL of parents and only three studies directly compared the QOL of parents of CWE and those with other chronic conditions. This presents an area of future research and would help identify the impact of epilepsy-specific factors on parental well-being, above and beyond the challenges and social limitations associated with rearing children with chronic conditions. In addition, only two studies used matched healthy controls; reliance on population norms has been found to bias estimates in other psychological constructs, and future studies should aim to carefully control for important sociodemographic variables and avoid relying on normative data [49]. Lastly, the objectives of the included studies varied, and the few studies evaluating predictors of parental QOL did not consistently report univariable and multivariable relationships.

The lack of consistent reporting by the studies included in this review prevented a meta-analysis of results and estimation of effect sizes. We were unable to provide estimates of the proportion of parents at risk of compromised QOL. We were also unable to rule out the possibility of publication bias. We would expect, however, that studies evaluating parental QOL would be publishable irrespective of 'positive' or 'negative' results.

There is clear evidence that parental psychological well-being and family environment are closely linked with children's QOL and mental-health [4-10]. Parents of CWE report unmet psychosocial care needs [50], with social and financial burden contributing to parents' feelings of being unable to manage their child's specific needs [37]. These parents report a need for ongoing

emotional support and education regarding the emotional and psychological impact epilepsy may have on their child, as well as difficulty with changes in family roles, unpredictability of seizures, and not knowing the long-term prognosis [51]. Education programs for CWE and their parents have been shown to improve self-management and communication skills, and reduced epilepsy-related concerns [52]. However, there is a severe lack of controlled trials of psychological treatments for children with epilepsy and their families [53]. Some programs have been recently developed, but await replication with larger samples in randomized controlled trials [54]. Interventions targeting the family as a unit are warranted, and healthcare providers should be aware of the interrelationships among epilepsy, family environment and the child's health and well-being. Beyond the implementation of family-centered care in the management of patients, there is evidence that problem solving therapy and parenting programs are effective and an important element in the management of chronic childhood illnesses for the health and well-being of the child and parent [11,55]. Parenting programs should focus on enhancing parent illness management skills, positive parenting skills, and reducing family stress [11]. Key elements of effective parenting programs include increasing positive interactions between parent and child, developing skills in communicating about emotions, increasing consistency and quality of parenting [11]. At a more fundamental level, acknowledgment of the impact that epilepsy has on parents may help to alleviate feelings of isolation. Connecting families with community support services, and instructing parents how to recognize the signs and symptoms of poor psychological well-being and where to access assistance for these issues may also be helpful. If parents are reminded of the importance of their own psychological well-being and can successfully identify these symptoms, they may be empowered to seek the appropriate resources, and improve their own well-being and that of their children.

Overall, this systematic review highlights the compromised QOL of parents of CWE, and the importance of psychosocial factors, which may have a larger impact on parental QOL relative to epilepsy-related factors. The majority of studies in this review found that parents of CWE have poorer scores across most domains of QOL, especially with regard to mental health-related QOL. We identified factors associated with parental QOL and highlighted a need for further research evaluating the potential causal relationship between parental QOL and family environment, psychosocial factors, coping strategies, management behaviors, and their child's QOL. Nonetheless, there is clear evidence that parental psychological well-being and family environment are closely linked with children's QOL and mental health. In managing chronic childhood illness, it is important to recognize the impact on the family, and the impact the family environment has on the health and well-being of the child.

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Figure 5-1. Flow chart of study selection.

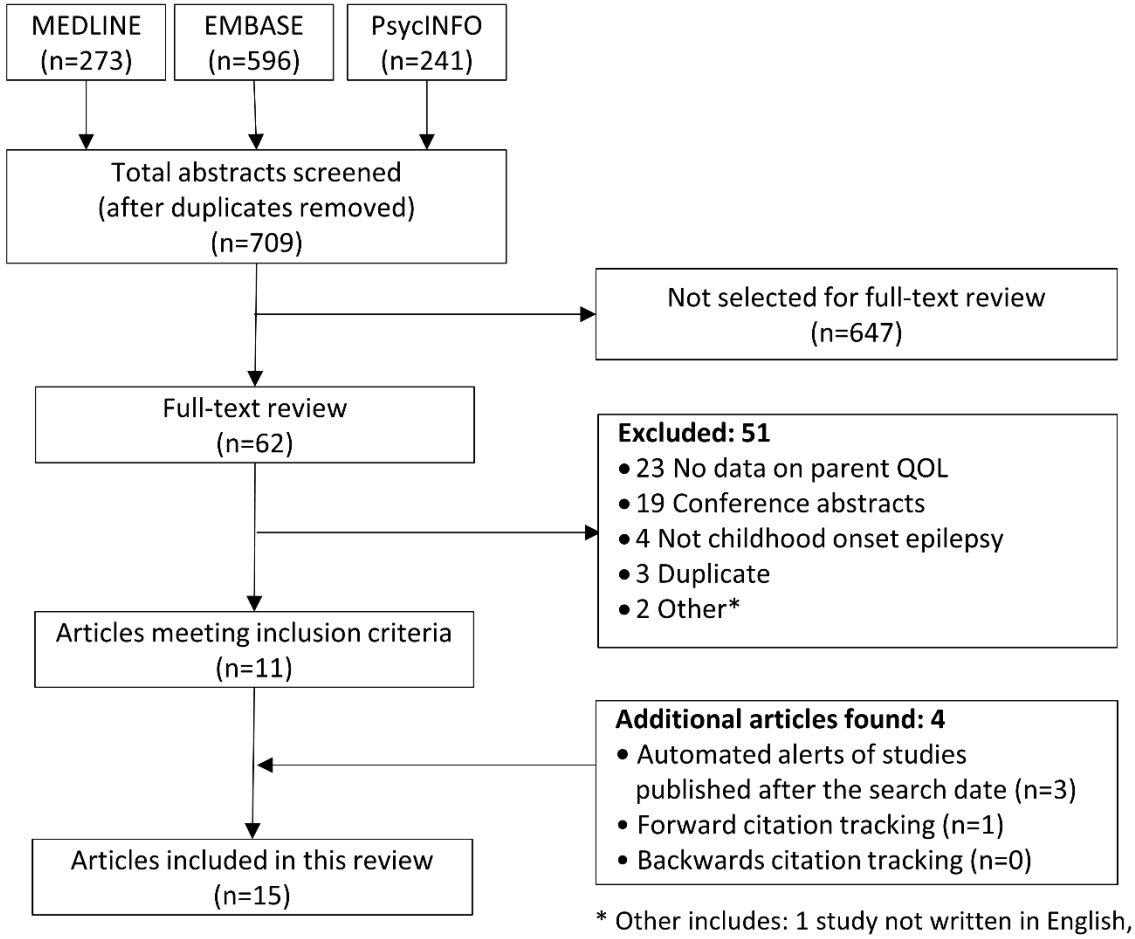

Table 5-1. Modified Downs & Black Quality Index

		Yes	No	Unclear
Reporting				
1.	Is the hypothesis/objective of the study clearly described?	1	0	0
2.	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	0	0
3.	Are the characteristics of the patients included in the study clearly described?	1	0	0
4.	Are the main findings of the study clearly described?	1	0	0
5.	Does the study provide estimates of the random variability in the data for the main outcome?	1	0	0
6.	Have actual probability values [or confidence intervals] been reported for the main outcomes except where the probability value is less than 0.001?	1	0	0
7.	Is the response rate clearly described?	1	0	0
External Validity				
8.	Were the patients asked to participate in the study representative of the entire population from which they were recruited?	1	0	0
9.	Were patients who were prepared to participate representative of the entire population from which they were recruited?	1	0	0
10.	Were the staff, places, and facilities where the patients were studied, representative of the treatment the majority of patients receive?	1	0	0
Interval Validity				
11.	If any of the results of the study were based on "data dredging," was this made clear?	1	0	0
12.	Were the statistical tests used to assess the main outcomes appropriate?	1	0	0
13.	Were the main outcome measures used valid and reliable?	1	0	0
14.	Was there adequate adjustment in the analyses from which the main results were drawn	1	0	0
Power				
15.	Did the study provide a sample size or power calculation to detect important effects where the probability value for a difference being due to chance is less than 0.05?	1	0	0

Note: The original 27-item Quality Index was modified to exclude assessment of items related specifically to intervention studies, including randomization, blinding, withdrawals and drop-outs, and intervention integrity, reducing it to 15 items

Table 5-2. Characteristics of studies reviewed.

Study	Study location	Study design	Source of recruitment	Inclusion criteria/ patient sample	Comparison group for this review
Reilly 2015 [22]	Sweden	CS	Multicentre; Hospitals	Surgical candidates	Population norms
Reilly 2017 [23]	Sweden	PR	Multicentre; Hospitals	Surgical patients	Population norms
Puka 2018 [24]	Canada	CS	Multicentre; Community	CWE w/o PNDD or major non-neurological disorder	Population norms
Lv 2009 [25]	China	CS	Single centre; Hospital	CWE w/o ID, PNDD, diseases other than epilepsy	Matched controls
Bompori 2014 [26]	Greece	CS	Single centre; Hospital	CWE w/o PNDD, NCD and patients seen because of seizure exacerbation	Matched controls
Mori 2017 [27-28]	Various	CS	International CDKL5 Disorder Database	Patients with CDKL5 mutation	Population norms
Gallop 2010 [29]	US, UK, Italy	CS	Clinics, support groups, websites	Patients with Lennox-Gastaut Syndrome	Population norms
Borusiak 2016 [30]	Germany	PR	Single centre; Hospital	New-onset epilepsy; excluded CWE w/ other disorders	Population norms
Moreira 2013[31], Carona 2014 [32]	Portugal	CS	Multicentre; Hospitals	CWE w/o comorbidities	Healthy controls
Mendes 2017 [33]	Portugal	CS	Multicentre; Hospitals	CWE w/o ID or other non-neurological condition	Other*
Bruce 2017 [34]	UK	PR	Single centre; Hospital	Intractable epilepsy; CWE starting the ketogenic diet	None
Soria 2012, [35] 2008 [36]	France	CS	Multicentre; Hospitals	All patients; excluded CWE with “occasional seizures”	None

* Normative data obtained from another study of controls from various European countries [56]; CS: cross-sectional; CWE: Children with epilepsy; ID: Intellectual disability; N/A: not available; NCD neurocutaneous disorders (eg. tuberous sclerosis); PNDD: Progressive neurodegenerative disorder; PR: prospective; UK: United Kingdom; US: United States; w/o: without.

Table 5-3. Summary of parent and patient characteristics.

Study	Parent factors			Child factors				
	n	Mothers, n (%)	Age	Females, n (%)	Age	Age at sz onset	Duration of sz	Current sz status
Reilly 2015 [22]	117 mothers 102 fathers		n/a	n/a	< 18 years	n/a	n/a	Intractable epilepsy
Reilly 2017 [23]	50 mothers 44 fathers		n/a	27 (54%)	< 20 years	3 [0 – 14]	n/a	25 (50%) sz free
Puka 2018 [24]	159	159 (100%)	49.2 (5.5) [35.6-69.4]	75 (47%)	18.1 (2.5) [12.9 – 23.9]	7.9 (2.3) [3.8 – 12.6]	10.2 (0.8) [8.6–11.6]	86% sz free ≥ 1 year 69% sz free ≥5years
Lv 2009 [25]	263	200 (76%)	39.5 (5.0)	96 (37%)	12.76 (4.0)	8.2 (4.4)	4.6 (3.9)	37% newly diagnosed 28% poorly controlled 35% well controlled
Bompori 2014 [26]	100	72 (72%)	n/a	42 (42%)	11 (2.6) [8 - 16]	6.0 (3.6) [0.1 - 14.5]	5.0 (3.2) [0.5–16]	74% Sz controlled
Mori 2017 [27]	158	141 (89%)	~ Median: 38.5 [24.6–63.7]	~ 85%	~ Median: 5.2 [0.2–34.1]	< 18 years*	n/a	~64% daily sz; 17% weekly sz; ~10% monthly/year sz; ~9% no sz
Gallop 2010 [29]	40	36 (90%)	43.0 [23–69]	15 (37%)	Median: 12 [4 - 43]	2.5 [0.1 – 7.5]	n/a	n/a
Borusiak 2016 [30]	36	n/a	n/a	16 (44%)	9.0 (4.2) [1 – 16]	9.0 (4.2) [1 – 16]	New-onset	n/a
Moreira 2013[31]	68	60 (88%)	42.4 (7.2)	33 (48%)	12.6 (2.9) [8 - 18]	< 18 years	5.6 (4.0)	On average sample was ‘a little to somewhat severe’
Mendes 2017 [33]	192	163 (85%)	41.5 (5.7) [29 – 58]	96 (50%)	11.9 (3.1) [8-18]	7.5 (3.6)	4.4 (3.4) [0.75 - n/a]	66% had no sz in past 9 months
Bruce 2017 [34]	12	n/a	n/a	n/a	Median: 3.5 [0.3 – 17]	n/a	n/a	n/a
Soria 2012 [35]	219	unclear	n/a	94 (43%)	10.5 (3.3) [3 – 16]	3.3 (2.9)	n/a	62% had ≤ 1 sz every 3 months 3.3% had ≥1 sz per day

Unless otherwise noted, all ages and durations are presented as mean years (standard deviation) [range]; n: sample size; sz: seizure; n/a: not available; *not stated explicitly; ~ denotes approximate value (data of entire cohort are presented, data from the subgroup with outcomes of interest are not available)

Table 5-4. Summary of the modified Downs & Black quality assessment.

Study	Total score (max = 15)	Reporting Quality (max = 7)	External Validity (max = 3)	Internal Validity (max = 4)	Power Calculation (max = 1)
Reilly 2015 [22]	12	6	2	4	0
Reilly 2017 [23]	14	7	3	4	0
Puka 2018 [24]	13	7	2	4	0
Lv 2009 [25]	14	7	3	4	0
Bompori 2014 [26]	12	5	3	4	0
Mori 2017 [27]	13	7	2	4	0
Gallop 2010 [29]	5	3	0	2	0
Borusiak 2016 [30]	13	7	2	3	1
Moreira 2013 [31]	12	6	2	4	0
Mendes 2017 [33]	14	7	3	4	0
Bruce 2017 [34]	7	5	0	2	0
Soria 2012 [35]	13	7	2	4	0
Mean:	11.7	6.2	1.8	3.6	0.1
Standard Deviation:	2.7	1.2	1.1	0.7	0.3

Table 5-5. Summary of study results.

Study	QOL measure	Scores relative to comparison group			Highlight of other study findings
		Poorer	Similar	Better	
Reilly 2015 [22]	SF-36 (Swedish norms)	MCS, MH, RE, SF, VT, GH^M, RP^M	PF, BP, GH^F, RP^F	PCS	Parental anxiety and depression associated with MCS
Reilly 2017 [23]*	SF-36 (Swedish norms)	MCS, VT, SF, MH^F, RE;	PCS, RP, GH, BP^M, MH^M, PF^M	BP^F, PF^F	MCS significantly improved for mothers and fathers post-surgery; PCS remained similar. Fathers had greater improvements in MCS relative to mothers. Improved PCS associated with reduced medications post-surgery.
Puka 2018 [24]	SF-12v2 (US norms)	–	MCS^M	PCS^M	Multivariable analyses: poorer QOL associated with poorer family environment, and greater maternal depressive symptoms/perception of stress
Lv 2009 [25]	SF-36 (Chinese norms)	PF, RP, BP GH, VT, SF, RE, MH	–	–	Multivariable analyses: parental anxiety, parental depression and poor seizure control had strongest impact on parental QOL
Bompori 2014 [26]	SF-12 (US norms)	MCS	PCS	–	Parents of CWE with a mild clinical presentation and no neurodevelopmental comorbidities had similar PCS and MCS relative to matched controls
Mori 2017 [27]	SF-12v2 (US norms)	MCS	–	PCS	Multivariable analyses: MCS --child's sleep disturbances, financial hardship and oral feeding (relative to enteral feeding) associated with poorer MCS; PCS-- oral feeding associated with better PCS.
Gallop 2010 [29]	SF-36v2 (US norms)	MCS (NTS)	–	PCS (NTS)	Qualitative data, highlighted social, physical, emotional, and financial impact on parents' QOL and the protective role of social support
Borusiak 2016 [30]	SF-12 (US norms)	MCS (NTS)	–	–	Evaluated a sleep monitoring intervention, finding no significant change in parental QOL 5-7 months after baseline
Moreira 2013[31]	EUROHIS-QOL-8	–	Overall QOL	–	Carona et al.[32]: Mediation model: parents' caregiving burden had a direct and indirect (through poor coping strategies [specifically, behavioral disengagement]) negative impact on QOL
Mendes 2017 [33]	EUROHIS-QOL-8	–	Overall QOL	–	Mediation model: family cohesion had a direct positive effect on parents' QOL; indirect effect (through perception of stigma) was not significant
Bruce 2017 [34]	Single item (scale 0-10)	–	–	–	Rating of 3.3 (SD 1.3; range 2 – 5) at baseline and 6.6 (SD 1.3; range 4 – 8) 12 months after ketogenic diet
Soria 2012 [35]	QOL Difficulties Questionnaire	–	–	–	Multivariable analyses: idiopathic epilepsy associated with better parental QOL; age, age at seizure onset, seizure frequency, number of medications, and school type were not significant.

PCS: physical component summary scale; MCS: mental component summary scale; PF: Physical functioning; RP: role limitation-physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role limitation-emotional; MH: mental health; NTS: not tested statistically; QOL: quality of life; ^{M} mothers only; ^{F} fathers only; * Scores at follow-up.

Table 5-6. Quality of life measures utilized by included studies

Scale	
SF-36: Short-form health survey	36-item scale. Generates 8 scales: Physical functioning, role limitation-physical, bodily pain, general health, vitality, social functioning, role limitation-emotional, and mental health. In addition, generates 2 composite scores relating to mental and physical health-related quality of life.
SF-12: Short-form health survey	12-item scale. Shortened version of the SF-36, which provides comparable composite scores. Generates 2 composite scores relating to mental and physical health-related quality of life. Although scores for the 8 scales can be calculated, it is recommended that they are not used.
WHOQOL-BREF: World Health Organization Quality of Life Instrument-Abbreviated Version	26-item scale. Generates a physical, psychosocial, environmental, and social summary score.
EUROHIS-QOL-8	8-item scale. Shortened version of the WHOQOL-BREF. Generates an overall score, and social, psychological, physical, and environmental subscale scores.
Parental QOL Difficulties Questionnaire	13-item scale. Generates a total QOL score.
Single item measure	1-item scale. “How does living with epilepsy and seizures affect your quality of life?” Scale of 0 to 10.

Table 5-7. Summary of bivariate relationships between parental quality of life and factors evaluated in at least two studies.

	Reilly [22]	Puka [24]	Lv [25]	Mori [27]	Moreira [31]	Mendes [33]	Soria [36]
Patient's sex (ref=female)		+		x		x	
Age of seizure onset		X	x				
Patient's age		X	X	x	x	x	
Seizure control		+	+	x		x	
Number of AMSs		x	X				
Parent's sex (ref=female)	+		X			+	+
Parent's age		X	−	+		x	
Greater parent education		X	X	x			
Parent full-time employment		+	−	x			
Higher income/SES		+	+	+		+	
Family size / # of siblings			x	+			
Parental depressive symptoms	−	−	−				
Parental anxiety symptoms	−		−				
Child's quality of life					+	+	

+ significant positive relationship; − significant negative relationship; x no significant relationship (p>.05)
SES: socioeconomic status; ASMs: antiseizure medications

Chapter 6: Health-related quality of life in mothers of children with epilepsy: 10 years after diagnosis [1]

6.1 Introduction

For the majority of individuals with childhood-onset epilepsy, the long-term prognosis for seizure control is generally favorable [1]. However, it is well recognized that the impact of epilepsy extends far beyond seizures, and the majority of children with epilepsy (CWE) have cognitive or psychiatric problems that may persist after seizure control [2,3]. Notably, such impairments may be particularly deleterious in childhood where they may interfere with the attainment of other cognitive, behavioral or social skills. Social outcomes in adulthood, such as education, employment, income, and independence, may be poor and are associated with cognitive and psychiatric comorbidities [4]. In terms of health related quality of life (HRQOL), the trajectory and long-term outcomes show improvements with time and are also associated with cognitive and psychiatric problems, as well as poor seizure control, continued use of antiseizure medications (ASM) and poorer family environment [5-7].

Although past research has evaluated multiple long-term outcomes following childhood-onset epilepsy, very little is known about parental outcomes. Relative to control groups, families of CWE fare worse on a range of factors, including the quality of the parent-child relationship, parenting confidence, family relationships, functioning and stress, and parental psychopathology [8]. In turn, these factors often have a greater negative influence on the child's HRQOL and psychopathology compared to epilepsy-related factors [8-12]. Although a number of cross-sectional studies have evaluated symptoms of depression and anxiety in parents of CWE [10,11],

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few have evaluated HRQOL. Studies evaluating parental HRQOL early in the course of the disorder have found poor HRQOL relative to population norms or control groups [13-17], although one study reported similar parental HRQOL [18]. Mothers in particular have been found to have poorer HRQOL relative to fathers of CWE [15]. Although a number of studies have evaluated the impact of childhood-onset epilepsy on parents, no studies, to our knowledge, have evaluated long-term outcomes [10,11].

Our first objective was (a) to describe the long-term HRQOL in mothers of CWE, and (b) to characterise the variation in observed HRQOL in relation to child, maternal, and family factors assessed at the ten-year follow-up. Our second objective was to evaluate the baseline child, maternal, and family factors predictive of maternal HRQOL ten years later. Mothers are often the primary caregiver, and understanding the determinants of maternal HRQOL is essential in identifying at-risk mothers and providing preventive interventions. Addressing the impact of childhood epilepsy on mothers is also essential for the well-being of the child because parental and family factors are thought to have a greater negative influence on the child's HRQOL and psychopathology compared to epilepsy-related factors [8-12].

6.2 Methods

6.2.1 Participants

Data come from a multicenter, prospective cohort of children with newly-diagnosed epilepsy, the Health-Related Quality of Life in Children with Epilepsy Study (HERQULES). The study protocol was approved by the research ethics boards at all participating sites. CWE were prospectively followed for a mean of ten years post-diagnosis. The details of the study design have been previously described [7]. Briefly, pediatric neurologists across Canada recruited

consecutive CWE meeting study inclusion criteria. Eligible children were aged four to twelve years with newly-diagnosed epilepsy (≥2 unprovoked seizures) and seen for the first time by a pediatric neurologist. Children were not eligible if they also had a diagnosis of other progressive or degenerative neurological disorder, or other major co-morbid non-neurological physical disorder likely to have an impact on quality of life (e.g., asthma requiring daily medication, renal failure). A total of 456 eligible children were identified; 373 (82%) primary care-giving parents, 346 of whom were mothers, participated by completing baseline evaluations. Data collection occurred at the time of diagnosis and 0.5, 1, 2, 8, and 10 years later. At the 10-year follow-up, 173 parents completed questionnaires. Since so few fathers were primary caregivers, we report baseline and 10-year follow-up data for the 159 mothers who completed the HRQOL questionnaire at follow-up.

6.2.2 Study Measures

The primary caregiver was asked to complete a mailed questionnaire at each time-point. Maternal HRQOL was measured using the second edition of the Short Form Health Survey (SF-12v2), a 12-item self-reported measure evaluating physical and mental health components of HRQOL over the past four weeks [19]. The psychometric properties of the SF-12v2 are well-established [19] and in this study, the internal consistency (as measured by Cronbach's alpha) was 0.90. Normative data from the United States (US) were used to calculate the T-score (mean 50, standard deviation 10) for the physical and mental health components of HRQOL. Difference scores were calculated by subtracting participants' scores from the US population mean of similarly aged women. These difference scores are used for all analyses; a positive difference score indicates that the participant rated their HRQOL as better relative to population norms.

6.2.2.1 Child and epilepsy factors

At baseline, mothers completed a questionnaire pertaining to their child's age and sex. At the 10-year follow-up mothers also reported on seizure status and whether their child was ever diagnosed with cognitive problems (developmental delay or learning disability), behavioral problems (conduct disorder, oppositional defiant disorder, or attention deficit hyperactivity disorder), emotional problems (anxiety or depression), or autism spectrum disorder. At the 10-year follow-up CWE, now aged 12.9 – 23.9 years, reported on whether they were currently taking ASMs. At baseline, neurologists completed a brief questionnaire providing information on the child's type and frequency of seizures, and comorbidities. Neurologists also completed the Global Assessment of Severity of Epilepsy (GASE) scale [20,21], a single item, 7-point Likert response scale providing an overall measure of the severity of epilepsy. The GASE has been shown to detect within-patient changes in severity of epilepsy and has moderate/strong correlations with several key clinical aspects of epilepsy [21]. Lower scores are indicative of greater severity; scores range from 1 (extremely severe) to 7 (not at all severe).

6.2.2.2 Maternal and family factors

At baseline and follow-up, mothers also completed a questionnaire inquiring about their age, sex, education, employment status, living arrangement, annual household income, and three self-reported measures of family environment. Family resources were evaluated using two subscales from the Family Inventory of Resources for Management (FIRM)[22] – specifically the family mastery and health subscale and extended family social support subscale. The 24 items in these scales use a four-point Likert scale with higher scores reflecting a more supportive, organized family environment with few disruptions in daily routines and interactions,

and greater extended family social support (scores range from 0 to 72). The FIRM has demonstrated adequate reliability and validity [22], and in this study, the internal consistency was α=0.90 at both baseline and follow-up. Family demands were evaluated using the Family Inventory of Life Events and Changes (FILE) scale [23]. This 71-item scale uses yes/no questions to evaluate the accumulation of normal and non-normal life events and changes in life events in the previous year. Scores range from 0 to 71, with higher scores reflecting greater demands. The FILE has well-established reliability and validity [23], and in this study, the internal consistency was α=0.81 and α=0.80 at baseline and follow-up, respectively. Lastly, satisfaction with family relationships was evaluated using the Family Adaptability, Partnership, Growth, Affection and Resolve (Family APGAR) scale [24]. This 5-item scale uses a five-point Likert scale with higher scores reflective of grater satisfaction with family relationships (scores range from 0 to 20). The APGAR has been found to be reliable and valid in clinical and research settings [24], and in this study, the internal consistency was α=0.89 and α=0.88 at baseline and follow-up, respectively.

6.2.2.3 Maternal psychosocial factors.

Mothers also completed the Center for Epidemiological Studies Depressive Scale (CES-D)[25] at baseline and follow-up, and the Perceived Stress Scale (PSS)[26] at follow-up. The CES-D is a 20-item self-reported measure of depressive symptoms over the past four weeks and uses a four-point Likert scale; total scores range from 0 to 60 with higher scores indicative of greater depressive symptoms. In this study, the internal consistency of the CES-D was α=0.91 and α=0.90 at baseline and follow-up, respectively. The PSS is a 10-item self-reported measure of perceived stress over the past four weeks using a five-point Likert scale; total scores range

from 0 to 40 with higher scores indicative of greater perceived stress. In this study, the internal consistency of the PSS was α=0.91.

6.2.3 Statistical Analyses

Analyses were conducted using SAS 9.4 (SAS Institute Inc. Cary, NC, USA) and SPSS 23.0 (IBM Corporation, Armonk, NY, USA). Prior to analyses, data were screened for missing values. Among the variables evaluated at follow-up, household income, whether the child was seizure-free in the past 5 years, and parental depressive symptoms had 4.7%, 2.3% and 0.6% missing data, respectively. Little's MCAR test indicated that the data were missing completely at random, $\chi^2(5) = 3.67$, $p = .60$. Among the variables evaluated at the time of diagnosis, household income, epilepsy severity, maternal depressive symptoms, and family demands had 4.4%, 3.1%, 0.6%, and 0.6% missing data, respectively. Little's MCAR test indicated that data were missing completely at random, $\chi^2(11) = 16.16$, $p = .14$. Multiple imputation, using the fully conditional specification method and five imputations, was used to account for missing data. The pooled R^2 and estimates from the five imputations are reported. Study findings were the similar when multiple imputation or complete case analyses were used.

Descriptive statistics computed for the sample included means and standard deviations (SD) for continuous variables, and frequencies and percentages for categorical variables. Independent samples *t*-tests or chi-squared analyses were used to compare the baseline characteristics of families that did and did not participate at the ten-year follow-up. To evaluate objective 1a (describing maternal HRQOL in the long-term), one-sample *t*-tests were used to evaluate whether the mean difference score of mothers' HRQOL relative to population norms was statistically different from 0. Next, we aimed to cross-sectionally evaluate the child

(including epilepsy syndrome), maternal, and family factors at follow-up (listed in Table 6-1) associated with mothers' HRQOL. A series of univariable simple linear regressions were used, and factors significant at $p<.20$ (selected *a priori* [27]) were entered into a three-stage block-wise linear regression. Stage 1 included child and epilepsy variables, as constructs considered to be the most distal to mothers' HRQOL. Stage 2 included maternal and family variables, and stage 3 included maternal psychosocial variables, considered to be the most proximal constructs to mothers' HRQOL. Since the maternal psychosocial factors may be considered closely related to HRQOL, a block-wise regression allowed for an evaluation of the impact of family factors on HRQOL, independent of maternal psychosocial variables. A similar set of analyses as those utilized for objective 1b were used to evaluate our second objective, to evaluate the baseline child, maternal, and family factors (listed in Table 6-1) predictive of mothers' HRQOL ten years later. The unstandardized regression coefficient (B) and the 95% confidence interval (CI) are presented; the omission of zero from the CI indicates a statistically significant effect at $p<.05$.

6.3 Results

Forty-six percent of the original sample of mothers (n=159) were included in this analysis. Children of these mothers had been diagnosed with epilepsy 10.2 years ago (SD: 0.8; range: 8.6 to 11.6). Mothers (94% were biological parent) had a mean age of 49.2 years (SD 5.5; range 35.6 to 69.4). At follow-up, 137 (86%) children had been seizure-free for at least one year, and 104 (69%) had been seizure free for at least five years. Child, maternal, and family characteristics at diagnosis and 10-year follow-up are presented in Table 6-1. We compared the baseline characteristics of families who were lost to follow-up with families who completed the 10-year follow-up. Families lost to follow-up fared worse on a number of factors at the time of

diagnosis; children had more comorbidities, and the mothers were younger, were less likely to live with their partner, had more depressive symptoms, and reported a poorer family environment (Table 6-2).

On average, scores on the physical and mental health components of mothers' HRQOL were 53.0 (SD 7.6; 95% CI 51.8, 54.2) and 49.5 (SD 9.3; 95%CI 48.0, 50.9), respectively. Relative to US population norms of women of the same age, the mean scores on physical and mental health component of mothers' HRQOL were 4.38 (SD 7.63; 95% CI 3.18, 5.58) and 0.16 (SD 9.33; 95%CI -1.29, 1.63) points higher (t_{158}= 7.24, p<.001 and t_{158}=0.23, p = .82), respectively. In our sample of mothers, 10 (6%) scored more than one standard deviation (SD) below population means on the physical health component of HRQOL, and 25 (16%) scored more than one SD on the mental health component of HRQOL. In comparison, in the population from which the norms are derived, 16% score more than one SD below the mean.

Results of univariable regressions are presented in Table 6-3. Block-wise linear regression models were used to evaluate the impact of child and epilepsy variables (Stage 1), maternal and family variables (Stage 2), and maternal psychosocial variables (Stage 3) on mothers' HRQOL (Table 6-4). The final model explained 10% of the variation in scores of the physical health component of HRQOL, and showed that better family resources was associated with higher (better) scores (B=0.20; 95%CI 0.03, 0.36). In terms of the mental health component of HRQOL, child and epilepsy variables (Stage 1) accounted for 8% of the variation in scores. Introducing maternal and family variables (Stage 2) accounted for 51% of the variation and introducing maternal psychosocial variables (Stage 3) accounted for 76% of the variation in scores. Higher household income, better family resources, better family functioning, and fewer family demands were all independent predictors of the mental health component of HRQOL.

Once parental depressive symptoms and perception of stress were introduced into the model, having a child without anxiety/depression (B=2.11; 95%CI 0.22, 3.99), better family functioning (B=0.34; 95%CI 0.06, 0.62), fewer depressive symptoms (B=0.33; 95%CI 0.20, 0.47), and perception of less stress (B=0.70; 95%CI 0.52, 0.88) were associated with better scores on the mental health component of HRQOL. In the final model, perception of stress was the strongest independent predictor of the mental health component of HRQOL.

A secondary objective of this study was to identify the baseline characteristics associated with maternal HRQOL 10-years after diagnosis. Univariable analyses are presented in Table 6-5. Results of the block-wise linear regression are presented in Table 6-6; only maternal depressive symptoms at baseline (B=0.35; 95%CI 0.16, 0.51) remained significantly associated with the mental health component of HRQOL ten years after diagnosis. Other variables were not significantly associated with HRQOL.

6.3.1 Sensitivity Analysis

Since the majority (86%) of CWE in our sample had been seizure–free for at least one year, we sought to investigate whether the relationships found above were similar for CWE who had experienced seizures in the past year. Due to the small sample size(n=22), only univariate associations were evaluated using simple linear regressions. Comparing mothers of children with and without seizures in the past year, the physical health scores (52.65 (SD 8.81) vs. 53.02 (7.38), p=.77, respectively) and mental health scores (45.88 (10.71) vs. 50.03 (9.00), p=.058, respectively) were similar. Overall, factors associated with HRQOL were similar in the sub-group that experienced seizures in the past year. Better family functioning (B=2.43; 95%CI 1.54, 3.32), fewer family demands (B=0.84; 95%CI 0.08, 1.61), child having been diagnosed with

behavioral problems (B=12.92; 95%CI 3.68, 22.23), fewer maternal depressive symptoms (B=0.86; 95%CI 0.63, 1.10), and maternal perception of less stress (B=1.15; 95%CI 0.70, 1.60) at the 10-year follow-up were associated with higher (better) scores on the mental health component of mother's HRQOL. There were no significant associations with the physical health component of mother's HRQOL.

6.4 Discussion

Although numerous studies have evaluated the long-term outcomes of children with epilepsy, there have been no studies, to our knowledge, evaluating the long-term impact on parents. Evaluating parental well-being is particularly important because epilepsy is known to negatively impact parental and family well-being, which in turn negatively impact the child's HRQOL and psychopathology [8-12]. The primary objective of this study was to describe the long-term impact of childhood epilepsy on mothers. We utilized a large population-based sample of CWE followed prospectively from diagnosis for ten years and evaluated mothers' HRQOL. Ten years after their child's diagnosis of epilepsy, the physical health component of mothers' HRQOL was significantly, though marginally, better compared to population norms of women of a similar age, whereas the mental health component of HRQOL was similar. As well, at the individual level, the proportion of mothers with scores lower than one standard deviation was smaller or similar than population norms. Family environment and maternal psychopathology were the most robust factors affecting mothers' HRQOL; child and epilepsy factors had little impact. These findings highlight the importance of addressing caregiver and family factors, which appear to have a greater impact on mothers' well-being, and consequently child well-being [8-12], than epilepsy factors.

Finding that mothers' physical and mental health component of HRQOL were the same or better compared to population norms ten years after diagnosis is encouraging given that nearly all studies evaluating CWE early in the course of the disorder find poorer parental HRQOL compared to the general population [13-17]. Changes in one's ratings of HRQOL may result from an improved health status or from one's adaptation to the disease [28]. Such an adaptation, known as response shift, is common and occurs when one's internal standards, values or conceptualization of HRQOL change as one adapts to the new health state [28]. In the current study, better ratings of the physical component HRQOL are likely associated with response shift as well as improved health status since the majority of children in our study had been free of seizures for more than five years.

Past studies have evaluated parental HRQOL early in the course of the disorder and have found that better parental HRQOL is commonly associated with seizure severity [13,14], duration of epilepsy [13], status epilepticus [13], the family's economic situation [13,29,30], family cohesion [30], perceived stigma [30], parental anxiety and depressive symptoms [13,15], parental coping behaviours [29,31], and parental burden and stress [31]. Though various studies have evaluated the role of child, parental or family factors, few studies have evaluated these factors simultaneously and in a comprehensive manner. The present study is therefore unique in evaluating HRQOL in the long-term and by evaluating multiple aspects of the family environment and maternal psychosocial functioning. We found that better family resources (family mastery and extended family social support) were predictive of better physical health related quality of life. All aspects of family environment assessed were significant predictors of the mental health component of HRQOL. When maternal psychosocial factors were added into the model, family functioning and maternal depressive symptoms and perception of stress

remained significant predictors. These findings are in keeping with other reports of parents' HRQOL early in the course of the disorder [13,15,29-31]. We found that mothers' perception of stress, as opposed to depressive symptoms, was the strongest predictor of poor mental health related quality of life. This may not be surprising given that perception of stress may encompass a number of factors evaluated in our model. In CWE, parental perception of stress has been associated with the child's functional status, social support, family cohesion, parental depression and coping behaviour [32]. In addition, parents of children with chronic conditions are commonly found to have higher levels of stress relative to parents of healthy children [33,34], and the use of more stress management strategies has been associated with better psychological health of caregivers [33]. Coping strategies may mediate the association between increased caregiving burden and impaired parental HRQOL [31]. These findings suggest that addressing caregiver burden may be a target for intervention in order to promote effective adaptation outcomes for parents and, subsequently, their children.

The second objective of this study was to evaluate the association between mothers' HRQOL in the long-term with child, maternal and family factors at the time of epilepsy diagnosis. We found that mothers' depressive symptoms at baseline were associated with mothers' HRQOL ten years later. This finding extends previous research reporting associations between parental depressive symptoms and HRQOL [13,15], and suggests that parental psychopathology at the time of diagnosis has long-term consequences. A substantial number of parents of CWE have unmet psychosocial care needs [35] and studies evaluating parents' needs report a desire for information regarding the effects of seizures and medications on their child's development, what to do when their child has a seizure, available support services, the opportunity to talk with other parents of CWE, emotional support and improved access to

healthcare providers [36,37]. Parents report that the most difficult aspects of parenting a child with epilepsy include changes in family roles, unpredictability of seizures, not having a long-term prognosis, need for ongoing emotional support, and need for education regarding the emotional and psychological impact epilepsy may have on their child [37]. In addressing these needs and difficulties, CWE and their families may benefit from family-centered care, in which care is planned around the entire family, with family members recognised as care recipients [38,39]. Family-centered care is associated with improved child and parental outcomes and can help families better manage the medical and non-medical aspects of their child's chronic condition, and thereby reduce commonly experienced challenges [39].

The findings of this study should be considered in light of the study's strengths and limitations. This is the first study, to our knowledge, to evaluate parental well-being in the long-term following a child's diagnosis of epilepsy. Mothers' HRQOL was measured using the short-form health survey (SF-12v2), a well-validated, reliable, and commonly utilized HRQOL instrument; nonetheless, this measure contains only 12 items and does not provide reliable subscale scores to evaluate other domains of HRQOL. In addition, HRQOL was only measured at the ten-year follow-up and not at baseline. As expected with any long-term study, attrition bias may have been introduced as a result of families being lost to follow-up. Similar trends are observed in other studies [40]. The majority of mothers (75%) were retained in the study through the four data collection points over the first two years of follow-up but, as one might expect given the lengthy follow-up period, attrition was higher (54%) by the final data collection 10 years after diagnosis. Of the families lost after the initial two years, we were unable to contact 52% of them, 17% had agreed to continue participating when contacted but did not return completed questionnaires, 8% indicated they were not interested any longer, and 7% offered

family issues as their reason for discontinuing. Families followed over the ten-year period had a better family environment and fewer maternal depressive symptoms at the time of diagnosis, and had children with fewer comorbidities, relative to mothers lost to follow-up. Thus, the current study may underestimate the proportion of mothers with poor HRQOL and limits the external validity of results. In addition, it is important to note that, at follow-up, the majority of youth in our study had been seizure-free for more than five years, which is representative of the course of epilepsy [1]. Although seizure-status was not associated with mothers' HRQOL in the current study, it will be important to evaluate whether these findings generalize to children with intractable epilepsy or continued seizures. It was the case in the current study, however, that results among the patients with continued seizures were similar to those without seizures and highlighted the impact of family environment and maternal depressive symptoms and perception of stress. In this subgroup, mothers of children who had been diagnosed with behavioral problems, had better mental health related quality of life. This finding may be attributable to the small sample size (6 out of 22 patients had behavioral problems) or it may be that, as a result of receiving a diagnosis of behaviour problems, these families have benefitted from interventions such as prescription medications for behavioral problems and/or receipt of more support through community services. Lastly, child comorbidities were not evaluated based on standardized measures.

Overall, the results of this study indicate that the long-term HRQOL for mothers of CWE is comparable to women of a similar age in the general population, and associated with family environment and maternal psychosocial factors. Epilepsy-related factors had little impact on mothers' HRQOL in the long-term. The results of this study are encouraging in showing favorable maternal HRQOL outcomes in the long-term and highlighting the important role of

modifiable factors on maternal HRQOL. Adopting family-centered care practises and addressing caregiver stress and burden may aid in proving vulnerable children and families with the support required to improve and maintain child and family well-being.

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Table 6-1. Parent reported child, maternal and family characteristics of participants at the time of diagnosis and at the 10-year follow-up.

	At diagnosis	At follow-up
Child variables	mean (SD) or n (%)	mean (SD) or n (%)
Sex, n female	75 (47%)	75 (47%)
Age, years	7.9 (2.3)	18.1 (2.5)
Aged <18 years	159 (100%)	83 (52%)
Epilepsy syndrome [a]		
Focal	94 (59%)	–
Generalized	65 (41%)	–
Seizure severity (GASE Score) [a, b]	5.5 (1.2)	–
Comorbidities at baseline [a, c]		
Cognitive problems	18 (11%)	–
Behavior problems	17 (11%)	–
Motor problems	6 (4%)	–
At least one of the above	29 (18%)	
Ever diagnosed with		
Cognitive problems	–	62 (39%)
Behavioural problems	–	33 (21%)
Emotional problems	–	39 (25%)
Autism spectrum disorder	–	11 (7%)
At least one of the above		84 (53%)
Seizure free >1 year	–	137 (86%)
Seizure free >5 years	–	107 (69%)
Not taking anti-epileptic medications	–	79 (72%)
Maternal and family variables		
Age, years	39.0 (5.3)	49.2 (5.4)
Has college/university level education	96 (60%)	113 (71%)
Works full time	113 (71%)	93 (58%)
Lives with partner	147 (92%)	140 (88%)
Household annual income		
<$50,000	36 (24%)	22 (15%)
$50,000-$99,999	70 (46%)	46 (30%)
$100,000-$149,999	46 (30%)	37 (25%)
>$150,000		46 (30%)
Family resources (FIRM)	53.2 (10.6)	52. (11.4)
Family demands (FILE)	8.4 (5.9)	8.1 (5.6)
Family functioning (APGAR)	14.5 (3.7)	14.8 (3.8)
Maternal psychosocial variables		
Depression Scale (CES-D)	11.9 (9.8)	9.8 (9.0)
Perceived Stress Scale	–	13.0 (7.3)

[a] Physician reported; [b] Lower scores reflect greater severity; score of 5 corresponds to 'somewhat severe'

Table 6-2. Baseline child, maternal and family characteristics of participants who did and did not participate at the ten-year follow-up.

	Lost to follow-up	Participated at 10-yr follow-up	
Child variables at baseline	mean (SD) or n (%)	mean (SD) or n (%)	p value
Sex, n female	103 (48%)	75 (47%)	.85
Age of first seizure, years	6.92 (2.5)	6.82 (2.5)	.70
Seizure severity (GASE)[a]	5.34 (1.2)	5.47 (1.2)	.30
Epilepsy syndrome, n			.75
Focal	114 (60%)	90 (59%)	
Generalized	80 (39%)	64 (41%)	
Physician reported:			
Cognitive problems	56 (27%)	18 (11%)	<.001
Behavior problems	39 (18%)	17 (11%)	.04
Motor problems	19 (9%)	6 (4%)	.05
At least one of the above	73 (35%)	29 (18%)	<.001
Maternal and family variables at baseline			
Age at baseline, years	37.55 (6.5)	38.97 (5.4)	.02
College/university level education, n	103 (48%)	96 (60%)	.02
Works full time, n	139 (65%)	109 (69%)	.47
Lives with spouse, n	176 (82%)	147 (92%)	.004
Household annual income, n			<.001
<$50,000	85 (43%)	36 (24%)	
$50,000-$99,999	79 (40%)	70 (46%)	
≥$100,000	34 (17%)	46 (30%)	
Family resources (FIRM)	47.67 (11.0)	53.24 (10.6)	<.001
Family demands (FILE)	10.29 (6.9)	8.44 (5.9)	.006
Family functioning (APGAR)	13.28 (3.7)	14.75 (3.7)	<.001
Maternal psychosocial variables at baseline			
Depression Scale (CES-D)	16.04 (10.3)	11.94 (9.8)	<.001

[a] Physician reported scale, lower scores are of indicative of greater seizure severity; 5 corresponds to 'somewhat severe' (scores range from 1 to 7).

Table 6-3. Univariable linear regression results evaluating the relationship between child, maternal, and family factors at follow-up with maternal HRQOL.

	Mental Health		Physical Health	
Child variables at follow-up	B (95% CI)	p-value	B (95% CI)	p-value
Sex, (ref=male)	-3.97 (-6.84, -1.10)	.007	-0.50 (-2.90, 1.91)	.68
Age	-0.12 (-0.71, 0.46)	.68	-0.13 (-0.61, 0.35)	.58
Focal seizures (ref=generalized)	-1.45 (-4.45, 1.55)	.34	0.47 (-1.98, 2.93)	.70
Ever diagnosed with				
Cognitive problems	-2.59 (-5.57, 0.39)	.09	-0.51 (-2.97, 1.95)	.68
Behavioural problems	1.11 (-2.5, 4.72)	.54	0.94 (-2.01, 3.9)	.53
Emotional problems	-3.34 (-6.71, 0.03)	.052	1.66 (-1.11, 4.44)	.24
Autism spectrum disorder	-0.81 (-6.48, 4.87)	.78	-1.84 (-6.25, 2.58)	.41
At least one of the above	-1.19 (-4.13, 1.74)	.42	-0.36 (-2.76, 2.05)	.77
Seizure free >1 year*	4.07 (-0.13, 8.27)	.058	0.52 (-2.95, 4.00)	.77
Seizure free >5 years	3.55 (0.40, 6.70)	.027	1.64 (-0.97, 4.26)	.22
Not taking anti-epileptic medications	-2.28 (-5.98, 1.41)	.22	-1.78 (-4.99, 1.43)	.27
Maternal and family variables at follow-up				
Age	-0.10 (-0.37, 0.17)	.46	0.1 (-0.12, 0.32)	.38
Has college/university level education	1.44 (-1.79, 4.67)	.39	1.16 (-1.48, 3.8)	.39
Works full time	2.99 (0.06, 5.93)	.046	1.05 (-1.37, 3.48)	.39
Lives with partner	-4.62 (-9.09, -0.16)	.042	-1.6 (-5.29, 2.09)	.39
Household annual income	2.73 (1.38, 4.09)	.0001	1.14 (-0.01, 2.28)	.051
Family resources (FIRM)	0.50 (0.39, 0.60)	<.0001	0.19 (0.09, 0.29)	.0002
Family demands (FILE)	-0.86 (-1.09, -0.64)	<.0001	-0.28 (-0.49, -0.07)	.010
Family functioning (APGAR)	1.45 (1.14, 1.76)	<.0001	0.25 (-0.06, 0.56)	.12
Maternal psychosocial variables at follow-up				
Depression Scale (CES-D)	-0.80 (-0.90, -0.69)	<.0001	-0.19 (-0.32, -0.06)	.004
Perceived Stress Scale	-1.05 (-1.16, -0.93)	<.0001	-0.19 (-0.35, -0.03)	.019

*In the multivariable model, seizure-freedom ≥ 1 year was not included because of its high correlation with seizure-freedom ≥ 5 years.

Table 6-4. Summary of block-wise linear regression evaluating the association between the physical and mental health components of mothers' HRQOL with patient and epilepsy factors (stage 1), maternal and family factors (stage 2) and maternal psychosocial functioning (stage 3). Unstandardized regression coefficients (B) and the 95% confidence interval (CI) are presented.

PATIENT AND FAMILY CHARACTERISTICS AT FOLLOW-UP:	Stage 1 B (95% CI)	Stage 2 B (95% CI)	Stage 3 B (95% CI)
Physical health HRQOL	n/a	R^2=.096, *p*=.004	R^2=.103, *p*=.01 R^2_{change} = .008, *p*=.54
Household annual income		0.45 (-0.75, 1.66)	0.40 (-0.84, 1.64)
Family resources (FIRM)		0.20 (0.05, 0.36) *	0.20 (0.03, 0.36) *
Family demands (FILE)		-0.09 (-0.34, 0.17)	-0.08 (-0.35, 0.19)
Family functioning (APGAR)		-0.22 (-0.62, 0.17)	-0.24 (-0.65, 0.18)
Maternal depressive symptoms			-0.11 (-0.32, 0.10)
Maternal perception of stress			0.11 (-0.17, 0.38)
Mental health HRQOL	R^2=.084, *p*=.009	R^2=.505, *p*<.001 R^2_{change} = .422, *p*<.001	R^2=.757, *p*<.001 R^2_{change} = .252, *p*<.001
Patient's sex (ref= male)	-3.59 (-6.43, -0.76) *	-1.06 (-3.26, 1.14)	-0.71 (-2.26, 0.85)
Seizure-free >5 years	2.34 (-1.00, 5.67)	-0.45 (-2.98, 2.08)	0.78 (-1.08, 2.64)
Has cognitive problems	-1.43 (-4.49, 1.63)	0.89 (-1.46, 3.23)	1.63 (-0.04, 3.29)
Has emotional problems	-1.7 (-5.22, 1.83)	-1.65 (-4.30, 1.01)	-2.11 (-3.99, -0.22) *
Mother employed		1.36 (-0.87, 3.59)	0.50 (-1.09, 2.10)
Mother lives with partner		-1.96 (-5.60, 1.69)	-0.07 (-2.66, 2.52)
Household annual income		1.36 (0.19, 2.54) *	0.27 (-0.58, 1.12)
Family resources (FIRM)		0.17 (0.03, 0.32) *	-0.08 (-0.19, 0.03)
Family demands (FILE)		-0.39 (-0.63, -0.16) *	-0.02 (-0.19, 0.16)
Family functioning (APGAR)		0.80 (0.42, 1.19) *	0.34 (0.06, 0.62) *
Maternal depressive symptoms			-0.33 (-0.47, -0.20) *
Maternal perception of stress			-0.70 (-0.88, -0.52) *

* highlights significant values

Table 6-5. Univariable linear regression results evaluating the relationship between child, maternal, and family factors at baseline with maternal HRQOL at follow-up.

	Mental Health		Physical Health	
Child variables at baseline	B (95% CI)	p-value	B (95% CI)	p-value
Age	0.25 (-0.40, 0.89)	.45	0.13 (-0.37, 0.63)	.61
Seizure severity (GASE Score)	-0.59 (-1.86, 0.68)	.36	0.83 (-0.22, 1.89)	.12
Comorbidities at baseline				
Cognitive problems	-0.76 (-5.39, 3.87)	.75	-0.17 (-3.95, 3.62)	.93
Behavior problems	1.73 (-3.02, 6.48)	.47	1.84 (-2.05, 5.72)	.35
Motor problems	-4.27 (-11.94, 3.40)	.27	-1.92 (-8.21, 4.36)	.54
At least one of the above	-0.55 (-4.35, 3.25)	.77	.44 (-2.66, 3.55)	.78
Maternal and family variables at baseline				
Age	-0.05 (-0.33, 0.22)	.71	0.15 (-0.07, 0.36)	.18
Has college/university level education	2.48 (-0.49, 5.46)	.10	2.71 (0.29, 5.12)	.028
Works full time	2.17 (-0.97, 5.31)	.18	-0.54 (-3.12, 2.04)	.68
Lives with partner	0.13 (-5.43, 5.68)	.96	-1.78 (-6.31, 2.75)	.44
Household annual income	2.52 (0.49, 4.55)	.015	2.42 (0.78, 4.05)	.004
Family resources (FIRM)	0.25 (0.12, 0.39)	.0002	0.1 (-0.01, 0.22)	.07
Family demands (FILE)	-0.45 (-0.69, -0.21)	.0003	-0.06 (-0.27, 0.14)	.54
Family functioning (APGAR)	0.48 (0.10, 0.87)	.015	0.19 (-0.13, 0.52)	.24
Maternal psychosocial variables at baseline				
Depression Scale (CES-D)	-0.41 (-0.54, -0.27)	<.0001	-0.03 (-0.15, 0.09)	.65

Table 6-6: Summary of block-wise linear regression evaluating the relationship between the physical and mental health component of mothers' HRQOL with baseline patient and epilepsy factors (stage 1), maternal and family factors (stage 2) and maternal psychosocial functioning (stage 3). Unstandardized regression coefficients (B), and the 95% confidence interval (CI) are presented.

PATIENT AND FAMILY CHARACTERISTICS AT BASELINE:	Stage 1 B (95% CI)	Stage 2 B (95% CI)	Stage 3 B (95% CI)
Physical health HRQOL	R^2=.017, *p*=.11	R^2=.0.084, *p*=.02 R^2_{change} = 0.053, *p*<.03	n/a
Seizure severity	0.84 (-0.18, 1.87)	0.64 (-0.38, 1.66)	
Mother's age		0.09 (-0.13, 0.31)	
Mother's education		1.85 (-0.61, 4.31)	
Household annual income		1.68 (-0.14, 3.50)	
Family resources (FIRM)		0.04 (-0.08, 0.16)	
Mental health HRQOL	n/a	R^2=.135, *p*=.001	R^2=.212, *p*<.001 R^2_{change} = .082, *p*<.001
Mother's education		1.17 (-1.82, 4.16)	0.97 (-1.89, 3.84)
Mother employed		2.70 (-0.39, 5.80)	2.40 (-0.56, 5.36)
Household annual income		0.87 (-1.31, 3.06)	0.88 (-1.26, 3.02)
Family resources (FIRM)		0.18 (-0.03, 0.38)	0.07 (-0.13, 0.27)
Family demands (FILE)		-0.29 (-0.58, 0.00)	-0.21 (-0.49, 0.07)
Family functioning (APGAR)		-0.14 (-0.64, 0.37)	-0.35 (-0.84, 0.15)
Maternal depressive symptoms			-0.34 (-0.51, -0.16) *

* highlights significant values

Chapter 7: Prevalence and trajectories of depressive symptoms among mothers of children with newly diagnosed epilepsy: A longitudinal 10-year study [1]

7.1 Introduction

It has become increasingly recognized that comorbidities associated with pediatric epilepsy are apparent very early in the course of the illness, with cognitive and psychiatric comorbidities evident before the first recognised seizure or the initiation of antiepileptic drugs[1-3]. Unsurprisingly, the elevated risk of comorbid disorders and poorer social outcomes last well into adulthood, and may remain even if seizures remit or are well controlled by medications[4-6]. Beyond the impact on patients, families of children with epilepsy (CWE) fare worse on a range of family factors relative to controls, including problems with family functioning and mental health problems among parents[7,8]. Recent systematic reviews have shown that parents of CWE have poorer quality of life relative to controls[9], and a significant proportion score above the clinical cut-off for major depressive disorder (up to 50% of mothers)[10] and anxiety (up to 58% of parents)[11]. Relative to fathers, mothers of CWE have also been found to have poorer quality of life, and more symptoms of anxiety, depression, and stress; however, it is unclear whether these differences are the result of sex differences or associated with being a primary caregiver[9,11-14]. Importantly, the literature to date indicates that poor family environment and parental mental health often have a greater impact on children's quality of life and health outcomes, relative to epilepsy-related factors[7,9-11,15-17]. Some studies have also found that various aspects of family environment act as mediators or moderators in the relationship between parents' mental health and children's quality of life[17]. Similarly, parents of children with

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developmental disabilities and non-neurological chronic conditions, such as asthma, are also at elevated risk for symptoms of depression and anxiety, with family and parent characteristics identified as robust factors associated with child well-being, rather than illness characteristics[18-20]. Therefore, understanding the impact of childhood illness on parents is important for the well-being of both children and parents.

Although the literature evaluating the family environment and parental well-being in families with CWE is growing, few studies have evaluated parental outcomes prospectively and very little is known about long-term outcomes. Past research evaluating these outcomes has come from the Health-Related Quality of Life in Children with Epilepsy Study (HERQULES)[16], which is also unique in that it focused on family environment. Family environment was described by household income and three standardized scales evaluating i) family demands/stressful events, ii) satisfaction with family relationships, and iii) family mastery and extended family social support. Mothers' depressive symptoms were prospectively evaluated at four time points over the first two years after their children's epilepsy diagnosis, and findings suggest that 30-38% of mothers scored in the at-risk range for major depressive disorder[21]. Mothers were a heterogeneous group, showing four distinct trajectories of depressive symptoms over time, which were associated with family environment, child cognitive problems and quality of life, and maternal age and education[21]. In addition, cross-sectional outcomes 10-years after diagnosis were recently published, finding that the quality of life for mothers of CWE was similar to population norms and associated with family environment and not epilepsy-related factors[22]. Notably, there have been no studies that have prospectively followed families of CWE over the long-term and evaluated any aspect of parental mental health or quality of life. Using data from HERQULES, we aimed to address this knowledge gap. The objectives of this

paper were to 1) identify the prevalence of depressive symptoms among mothers of CWE at the time of diagnosis, and 0.5, 1, 2, 8, and 10 years later, 2) identify trajectories of mothers' depressive symptoms, and 3) identify the baseline child, maternal, and family characteristics associated with depressive symptom trajectories.

7.2 Methods

7.2.1 Participants

Data presented here were collected as part of the HERQULES study, a prospective cohort of children with newly diagnosed epilepsy. Ethics approval was obtained from relevant research ethics boards, and parents provided written consent. Details of the study design have been described previously[16]. Briefly, pediatric neurologists across Canada recruited consecutive patients meeting inclusion criteria: children aged 4-12 years of age with newly diagnosed epilepsy (≥2 unprovoked seizures) and seen for the first time by a pediatric neurologist. Children were not eligible if they also had a diagnosis of other progressive or degenerative neurological disorder, or other major comorbid non-neurological physical disorder likely to have an impact on quality of life (e.g., asthma requiring daily medication, renal failure).

A total of 456 eligible children were identified, and 373 (82%) participated in the study. The parent primarily responsible for the child's daily care and the child's neurologist were asked to complete questionnaires at six-time points: at the time of epilepsy diagnosis (baseline), and 0.5, 1, 2, 8, and 10 years later. Because few fathers completed the survey at multiple time points (n=12), only surveys completed by mothers (biological, adoptive, or foster; n=356) were included in these analyses.

7.2.2 Measures

The primary outcome of interest was mothers' depressive symptoms, as measured by the Center for Epidemiological Studies Depression Scale (CES-D)[23,24]. The CES-D is a 20-item self-reported measure that assesses mood, somatic complaints, interactions with others, and motor functioning over the past week. The scale uses a 4-point Likert scale (0-3) with total scores ranging from 0 to 60. Higher scores are indicative of greater depressive symptoms, and scores of 16 or higher are indicative of being at-risk for major depressive disorder. In this study the internal consistency of the CES-D ranged from 0.90 to 0.92 across the six time points.

6.2.2.1 Child Characteristics

Mothers reported on their child's age and sex, and the child's neurologist reported the type of seizures (focal vs generalized), severity of epilepsy, and the presence of behavioral, cognitive, or motor problems. Severity of epilepsy was measured using the Global Assessment of Severity of Epilepsy (GASE) scale, a single item, 7-point Likert response scale[25,26]. The GASE has been shown to detect within-patient changes in severity of epilepsy and has moderate/strong correlations with several key clinical aspects of epilepsy[25,26]. In these analyses, the GASE was reverse coded, such that lower scores are indicative of greater severity. Scores on the GASE ranged from 1 to 7, corresponding to "extremely severe", "very severe", "quite severe", "moderately severe", "somewhat severe", "a little severe", and "not at all severe", respectively.

7.2.2.2 Parent and Family Characteristics

Mothers reported on their age, educational background, employment status, and whether they were living with a partner. Family environment was evaluated using mothers' report of their household income and three standardized scales. The Family Inventory of Life Events and Changes (FILE) was used to evaluate family demands[27]. The FILE is composed of 71 yes/no questions evaluating the accumulation of normal and non-normal life events and changes in life events in the previous year. Scores range from 0 to 71 with higher scores indicative of greater demands. In this study the internal consistency of the FILE was $\alpha = 0.84$. The Family Adaptability, Partnership, Growth, Affection and Resolve (Family APGAR) scale was used to evaluate family functioning[28]. The Family APGAR is composed of 5 items using a 5-point Likert scale, with higher scores indicative of greater satisfaction with family relationships. Scores range from 0 to 20, and in this study the internal consistency of the Family APGAR was $\alpha = 0.87$. Lastly, the Family Inventory of Resources for Management (FIRM; specifically, the family mastery and health subscale, and the extended family social support subscale) was used to evaluate family support resources[29]. The 24 items in these subscales use a 4-point Likert scale with higher scores indicative of more supportive, organized family environment with few disruptions in daily routines and interactions, and greater extended family social support. Scores range from 0 to 72, and in this study the internal consistency of the FIRM was $\alpha = 0.90$.

7.2.3 Statistical Analyses

All analyses were conducted using SAS 9.4 (SAS Institute Inc. Cary, NC, USA). Descriptive statistics computed for the sample included means and standard deviations (SD) for continuous variables, and frequencies and percentages for categorical variables. The GASE and

household income (each with ≥6 categories) were treated as continuous variables to obtain a more parsimonious model (results were similar when treated as categorical variables). Univariable logistic regression models were used to compare the baseline characteristics of families that completed the 10-year follow-up with those who did not.

Trajectories of mothers' depressive symptoms over the 10-year period were investigated using latent class growth modeling, using the Proc Traj macro [30]. This semi-parametric approach identifies distinct subgroups of individuals following a similar pattern on an outcome over time, in this case depressive symptoms. The number of trajectory groups is guided by *a priori* expectations, overall model fit as assessed by the Bayesian Information Criterion (BIC), posterior probability, odds of correct classification, and proportion of individuals in each group [31]. Models with a different number of groups were compared using an estimate of the log Bayes Factor, which is approximately equal to two times the difference in the BIC values for the two models being compared; values ranging from 0 to 2 are interpreted as weak evidence for the more complex model (the model with the additional group), values ranging from 2 to 6 are interpreted as moderate evidence, values ranging from 6 to 10 are interpreted as strong evidence, and values greater than 10 are interpreted as very strong evidence for the more complex model [30]. First, cubic trajectories were specified for one group then additional groups were added until the model worsened[30]. Once the number of groups was determined, non-significant cubic or quadratic terms were removed to ensure model parsimony. Results were consistent when a different set of start values was used. We used a censored normal model and an extension to account for non-random attrition, with intermittent missing data assumed to be missing at random [32]. The extension for non-random attrition allows for the joint estimation of depressive symptom trajectories and probability of dropping out. The probabilities of group membership

and attrition are not assumed to be independent and the probability of dropout was allowed to vary as a function of the prior observation [32].

Once the groups were finalized, we compared the *baseline* child, maternal, and family characteristics of the mothers in each trajectory group. Analysis of variance and post hoc Tukey correction was used for continuous variables. Categorical data were evaluated using the chi-square or Fishers' exact test. A multinomial logistic regression model was used to identify factors associated with each trajectory group. Only variables significant at $p<0.20$ in the bivariate comparisons were included in a multivariable model. Listwise deletion was used for missing data, as only 6% of the sample (n=22) were missing data on the variables of interest.

7.3 Results

A total of 356 mothers were included in this study. The CES-D was completed by 344 mothers at baseline, 316 at 6 months, 282 at 1 year, 259 at 2 years, 181 at 8 years, and 159 at 10-year follow-up. Mothers (94% were biological parent) completed questionnaires. Table 7-1 presents a summary of the child, maternal, and family characteristics. On average, mothers were 38.1 years of age at diagnosis (SD 6.2; range 24 to 71), and 49.1 years at the 10-year follow-up (SD 5.4; range 36 to 69). Their children had a mean age of 7.9 years at diagnosis (SD 2.4; range 4 to 12.8) and 18.1 years at the 10-year follow-up (SD 2.5; range 13 to 24). At the time of diagnosis, the majority of children had a 'somewhat severe' (23%) or 'a little severe' (36%) epilepsy severity score on the GASE, and 28% of children had cognitive, behavioral, or motor problems. At the 10-year follow-up, 71% of children had not received epilepsy care from a physician in the prior year and therefore, we could not obtain physicians' report of clinical

characteristics. At the 10-year follow-up, the majority of children (68%) had been seizure-free for at least 5 years.

At the last follow-up, data were collected from 159 mothers, out of the total of 356. We compared the baseline characteristics of families who were lost to follow-up with families who completed the 10-year follow-up. Families lost to follow-up fared worse on a number of factors at the time of diagnosis: children had more comorbidities, and the mothers, who were younger, were less likely to be living with a partner, had poorer educational attainment, reported a poorer family environment, and had more depressive symptoms (Table 7-2). Non-random attrition was controlled for in modeling the trajectories of depressive symptoms over time[32].

7.3.1 Prevalence of Depressive Symptoms

Mothers' mean CES-D score was 14.5 (SD 10.5) at baseline; 11.6 (SD 9.5) at 6 months; 12.2 (SD 9.7) at 1 year; 11.9 (SD 10) at 2 years; 11.2 (SD 9.6) at 8 years; and 9.8 (SD 9.0) at 10 years. The period prevalence of being in the at-risk range for major depressive disorder, as defined by scoring ≥ 16 [23] in at least one of the six time points evaluated, was 57% (n=204). At baseline, 38% of mothers scored in the at-risk range for major depressive disorder, which changed to 29% at 6 months, 32% at 1 year, 29% at 2 years, 27% at 8 years, and 24% at 10 years. Because some mothers were lost to follow-up, we also evaluated the CES-D scores of those mothers who were followed for the entire 10-year period. We found a similar trend, where the mean CES-D was 12.3 (SD 9.9) at baseline, 9.7 (SD 8.8) at 6 months, 11.0 (SD 9.1) at 1 year, 10.5 (SD 9.2) at 2 years, 11.0 (SD 9.7) at 8 years, and 9.8 (SD 9.0) at 10 years. At baseline, 30% of this subsample scored in the at-risk range for major depressive disorder, which changed to 23% at 6 months, 27% at 1 year, 23% at 2 years, 25% at 8 years, and 23% at 10 years.

7.3.2 Trajectories of Depressive Symptoms Over Time

Depressive symptoms over time were best fitted by a four-class model with linear and quadratic terms (Table 7-3). Figure 7-1 presents the trajectory of each group. In addition, Figure 7-2 presents each mothers' trajectory, Table 7-4 presents the estimates of the trajectory parameters, and Table 7-5 presents the estimated CES-D score at each time point. The first group (29% of the sample; labeled *Low-Stable*) identified mothers with few depressive symptoms (CES-D scores of ~ 6) throughout the 10-year period. The second group (46%; *Intermediate-Stable)* is composed of mothers with elevated depressive symptoms relative to the *Low-Stable* group, with CES-D scores below the at risk range (scores of ~12), that remained stable over the 10-year period. The third group (20%; *High-Stable*) is composed of mothers with depressive symptoms in the at-risk range for major depressive disorder (CES-D scores of ~23) that remained stable over the 10-year period. Lastly, the fourth group (5%; *High-Decreasing*) is composed of mothers with high CES-D scores at baseline (score of ~38) that declined over the 10-year period (CES-D scores of ~5 at the 10-year follow-up).

7.3.3 Factors Associated with Each Trajectory

Child, maternal, and family characteristics at the time of diagnosis were compared across the four trajectory groups and results are summarised in Table 7-6. Mothers with a more positive family environment (income, support resources, demands, and functioning), who were older, lived with their partner, had a college/university education, and had a child without a cognitive comorbidity at the time their child was diagnosed were more likely to have a better trajectory of depressive symptoms over time. Table 7-7 presents the results of the multivariable model,

presenting the odds ratio and using the *Low-Stable* group as the reference category. Better family environment (namely, greater family resources [e.g. family mastery and social support], and better family functioning [e.g. satisfaction with family relationships]) was consistently associated with a better trajectory of depressive symptoms over time. In addition, the *Intermediate-Stable* group was more likely to have children with focal seizures (relative to generalized) and cognitive problems. The *High-Stable* group was more likely to have children with cognitive problems, and mothers were younger and less likely to have a college or university level education.

7.4 Discussion

This was the first study, to our knowledge, to prospectively evaluate any aspect of mental health or quality of life among parents of CWE in the long-term, and determine whether the course of parental mental health in the long-term mirrors the favorable long-term course of seizure control. Epilepsy is known to negatively impact parental mental health and the family system, which in turn negatively impacts children's mental health and well-being[7,9-11,15-17]. We found that 38% of mothers scored in the at-risk range for major depressive disorder at the time of epilepsy diagnosis, compared to 24% at the 10-year follow-up. Mothers of CWE were not a homogenous group; four subgroups with unique trajectories of depressive symptoms over a ten-year period were identified. Better family environment (namely, greater satisfaction with family relationships and greater family mastery and social support) at the time of diagnosis was consistently associated with better long-term trajectories of depressive symptoms. Children's cognitive problems and type of seizures, and mothers' age and education were also associated with the trajectory of depressive symptoms. Notably, these child and maternal factors are largely unmodifiable, lending more support for future interventions to focus on family environment.

We found that almost all mothers showed a stable trajectory of depressive symptoms over time, scoring similarly at the time of diagnosis and throughout the 10-year follow-up. This is particularly interesting given that, at final follow-up, 68% of the adolescents and young adults (AYA) had been seizure-free for more than five years. This indicates that the course of mothers' depressive symptoms may not be associated with the course of seizure control. Considering the needs of parents, this finding is not unexpected. Parents report unmet psychosocial care needs [33] and a need for more information, ongoing emotional support, school support, and dealing with changes in family roles [34,35]. Additionally, given that the trajectories were associated with family environment at the time of diagnosis, these findings highlight the long-lasting and persistent effects of the family system.

Evidence-based treatments for depression, such as cognitive behavioral therapy and pharmacotherapy, are warranted to improve depressive symptom trajectories among parents of CWE. However, beyond the implementation of established treatments, there is an opportunity for psychobehavioral interventions that go beyond focusing on the individual and target children, parents, and other family members. The severity of illness and child care needs are important contributors to the mental health of parents of children with neurodevelopmental conditions, however a number of important intermediaries may be targeted [36,37]. For example, the use of stress management and coping strategies are associated with better parental mental health and have been found to mitigate the impact of caregiving burden on parents' mental health [38-40]. Notably, targeting the whole family system would additionally contribute to improving children's mental health. In children, family mastery and support resources have been found to moderate the relationship between severity of epilepsy and the child's emotional well-being [41]. Interventions (e.g. mindfulness-based or self-management interventions) that may be delivered

by non-clinical staff, in groups, and in a community setting may be optimal in reducing costs and allowing for wide-spread utilization. This effort may also be supported by collaboration with community-based epilepsy support agencies well-equipped to provide support to patients and with their families. Although there is some evidence of improved outcomes following family-based interventions [35,42,43], there is a need for larger, randomized controlled trials.

In evaluating the results of the current study, a number of limitations should be considered. First, as with any latent class growth model, the four identified trajectories are an approximation of a more complex reality, and do not necessarily represent distant entities. As indicated in Figure 7-2, depressive symptoms fluctuate over the long-term, with some mothers scoring above the cut-off for major depressive disorder, for the first time, years after their child's diagnosis of epilepsy. Indeed, we found that 10% and 9% of mothers had scored above cut-offs for risk of major depressive disorder, for the first time, at the 8 and 10-year follow-up, respectively (data not shown). Although these incidence proportions may not be associated with epilepsy, this finding nonetheless emphasizes the importance of discussing the possibility of the late emergence of mental health problems for parents of CWE. This is particularly because their child may not be under regular review by their physician and there may not be an opportunity to raise questions about the parents' well-being. Second, although a strength of this study was the prospective evaluation of mothers' depressive symptoms into the long-term, the study was inevitably affected by attrition; at the 10-year follow-up, 45% of the sample completed questionnaires. The majority of mothers (75%) were retained in the study over the first 2 years of follow-up, with the majority of attrition occurring at the 8- and 10-year follow-up. Of the families lost after the initial 2 years, we were unable to contact 52% of them, 17% had agreed to continue participating when contacted but did not return completed questionnaires, 8% indicated

that they were not interested any longer, and 7% offered family issues as their reason for discontinuing. We found that families lost to follow-up fared worse on a number of factors at the time of diagnosis, including maternal depressive symptoms. This suggests that our report may underestimate the proportion of mothers at risk for major depressive disorder. It is important to note, however, that the analyses we used attempted to account for this non-random attrition. We also had not collected information on whether mothers had received any treatments for mental health problems; it may be possible that the *High-Decreasing* trajectory group received treatment (as a result of endorsing many depressive symptoms at baseline) which subsequently resulted in remission of depressive symptoms in the long-term. Third, the measure of depressive symptoms utilized (the CES-D), is reliable and well-validated but, unlike the revised version (CESD-R released *after* the initiation of this study), does not include the additional response option that allows for the determination of whether individuals meet Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for major depressive disorder. Future studies should evaluate the proportion of mothers meeting DSM criteria for major depressive disorder and the factors contributing to the maintenance of depressive symptoms in the long-term and whether family factors act as mediators or moderators in the relationship between epilepsy-specific factors and the mental health outcomes of parents. Lastly, the majority of AYA in our study had been seizure-free for more than 5 years at final follow-up, which is representative of the reported course of epilepsy[5]. It will be important for future studies to evaluate the trajectory of mothers' depressive symptoms in samples with continued or refractory seizures.

This study delineated the prevalence and trajectories depressive symptoms among mothers of CWE from diagnosis over a 10-year period. Although depressive symptoms decreased over time as a group, the trajectory analyses showed that almost all mothers showed a

stable trajectory over time, scoring similarly at the time of diagnosis and throughout the 10-year follow-up. The stability in depressive symptoms over the 10-year period, despite favorable seizure outcomes, highlights the need for targeting parental mental health, possibly through family-focused interventions. We found that better family environment, epilepsy-specific factors, and maternal age and education at baseline were associated with depressive symptoms trajectories over the 10-year period. Given the strong evidence that parental and child health and well-being are closely linked, greater recognition of the impact of epilepsy on parents and the family is needed.

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Figure 7-1. Estimated trajectories of mothers' depressive symptoms during the first 10 years after their child's diagnosis of epilepsy.

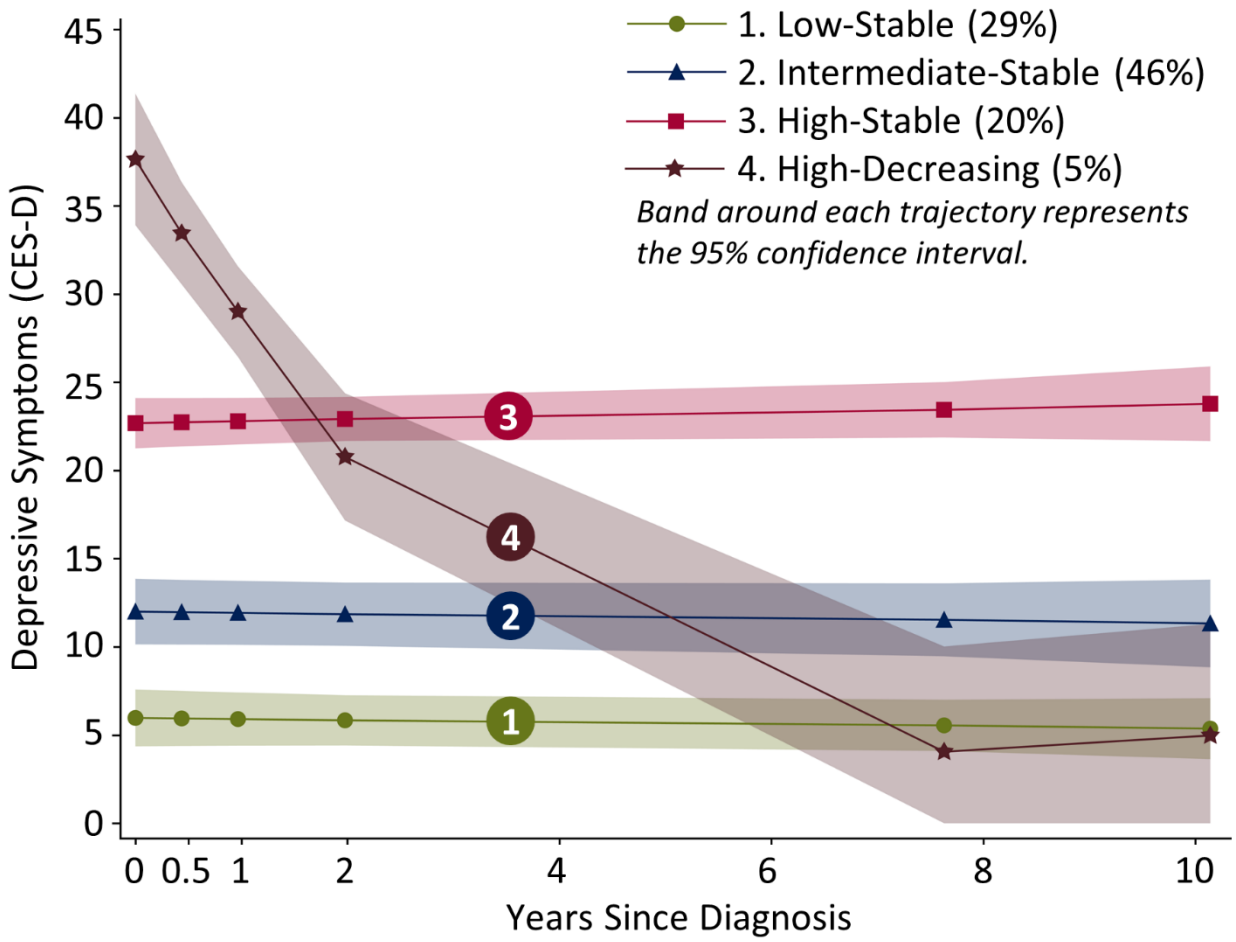
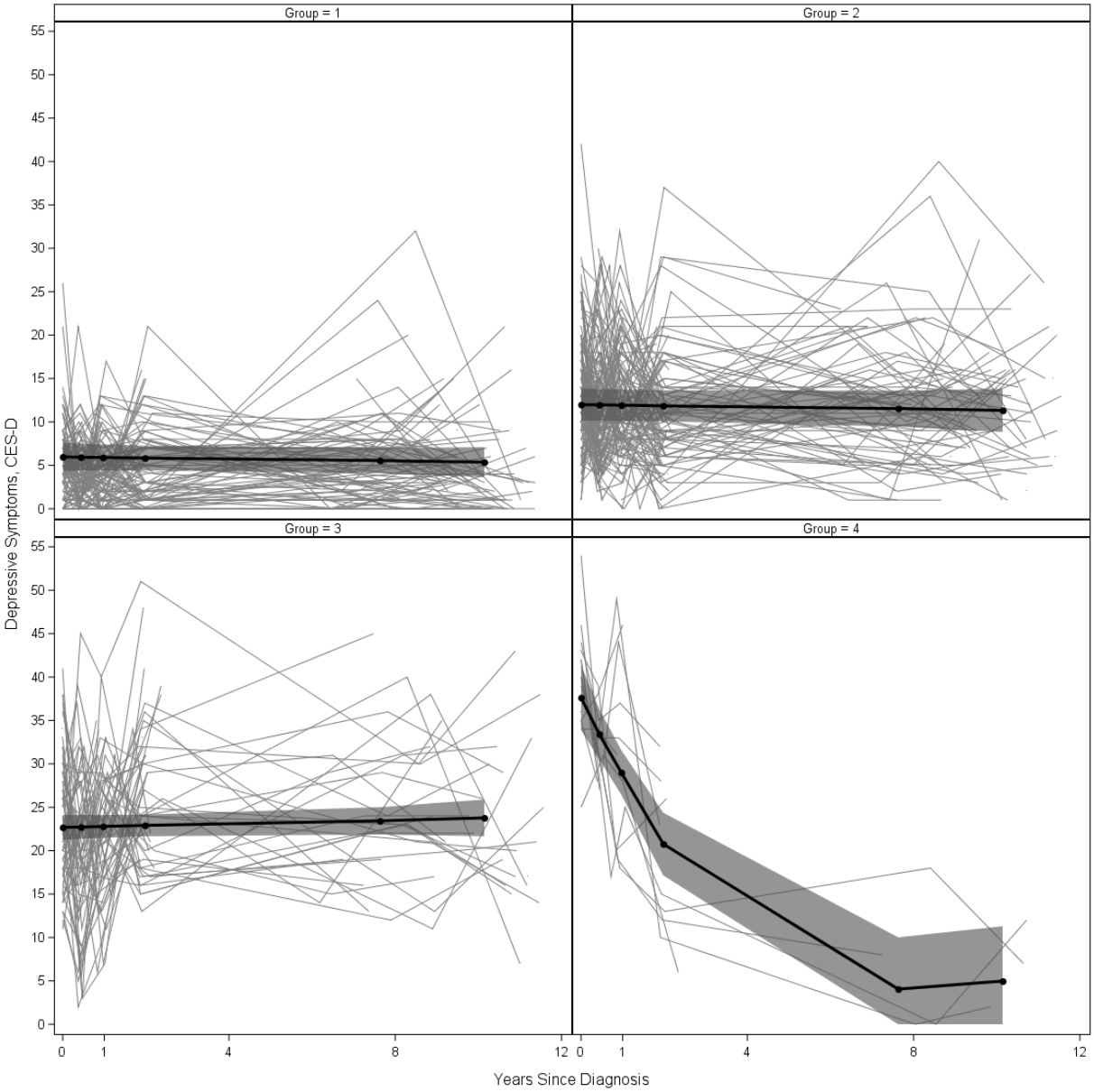


Figure 7-2. Trajectories of mothers' depressive symptoms during the first 10 years after having a child diagnosed with epilepsy.



Note: Thick solid lines and band depict predicted trajectories and 95% confidence interval. Light lines depict observed trajectory for each individual.

Table 7-1. Parent reported child, maternal and family characteristics at diagnosis (n=356) and at the 10-year follow-up (n=159).

Characteristics	At Diagnosis Mean (SD) or n (%)	10-Year Follow-up Mean (SD) or n (%)
Child		
Sex, n female	171 (48%)	75 (47%)
Age, years	7.9 (2.4)	18.1 (2.5)
Focal seizures [a, b]	212 (61%)	–
Epilepsy severity, GASE [a]	5.4 (1.2)	–
Seizure free >1 year	–	133 (86%)
Seizure free >5 years	–	106 (68%)
Comorbidities [a]		
Cognitive	71 (20%)	–
Behavioral	55 (15%)	–
Motor	23 (6%)	–
At least one of the above	98 (28%)	–
Maternal		
Age, years	38.1 (6.2)	49.1 (5.4)
Living with partner	309 (86%)	138 (87%)
Works full or part time	236 (67%)	123 (78%)
College/university education	190 (53%)	113 (72%)
Family		
Annual Household Income		
< $20,000	9 (8%)	2 (1%)
$20,000 - $39,999	50 (14%)	15 (10%)
$40,000 - $59,999	74 (21%)	12 (8%)
$60,000 - $79,999	63 (18%)	19 (13%)
$80,000 - $99,999	49 (14%)	19 (13%)
$100,000 - $149,999	82 (24%)	37 (25%)
≥ $150,000		46 (31%)
Resources, FIRM	50.1 (11.1)	52.0 (11.5)
Demands, FILE	9.5 (6.6)	8.1 (5.6)
Functioning, APGAR	13.9 (3.8)	14.8 (3.9)

[a] Physician reported

[b] Unknown/undetermined for six children; reference category is generalized seizures

Table 7-2. Baseline characteristics of participants that did (n=159) and did not (n=197) complete the 10-year follow-up.

Baseline characteristics	Completed 10-year follow-up Mean (SD) or n (%)	Did not complete 10-year follow-up Mean (SD) or n (%)	Odds Ratio (95% CI) [a]
Child			
Sex, n female	75 (47%)	96 (49%)	1.07 (0.70, 1.62)
Age, years	7.95 (2.3)	7.94 (2.4)	1.00 (0.91, 1.09)
Focal seizures [b, c]	93 (59%)	119 (62%)	1.14 (0.74, 1.75)
Epilepsy severity, GASE [b]	5.49 (1.17)	5.33 (1.2)	0.89 (0.74, 1.07)
Comorbidities [b]			
Cognitive	17 (11%)	54 (27%)	3.15 (1.74, 5.70) *
Behavioral	17 (11%)	38 (19%)	2.00 (1.08, 3.69) *
Motor	5 (3%)	18 (9%)	3.10 (1.12, 8.54) *
At least one of the above	29 (18%)	69 (35%)	2.42 (1.47, 3.98) *
Maternal			
Age, years	38.99 (5.35)	37.33 (6.65)	0.96 (0.92, 0.99) *
Living with partner	147 (92%)	162 (82%)	0.38 (0.19, 0.76) *
Works full or part time	108 (68%)	128 (66%)	0.92 (0.59, 1.43)
College/university education	98 (62%)	92 (47%)	0.55 (0.36, 0.83) *
Depressive symptoms, CESD	16.2 (10.62)	12.26 (9.89)	1.04 (1.02, 1.06) *
Family			
Annual Household Income			
< $20,000	4 (3%)	25 (13%)	0.73 (0.63, 0.84) *
$20,000 - $39,999	15 (10%)	35 (18%)	
$40,000 - $59,999	34 (22%)	40 (21%)	
$60,000 - $79,999	28 (18%)	35 (18%)	
$80,000 - $99,999	29 (18%)	20 (11%)	
≥$100,000	47 (30%)	35 (18%)	
Resources, FIRM	53.18 (10.7)	47.55 (11.0)	0.95 (0.93, 0.97) *
Demands, FILE	8.43 (5.9)	10.45 (7.0)	1.05 (1.02, 1.09) *
Functioning, APGAR	14.74 (3.7)	13.28 (3.7)	0.90 (0.85, 0.95) *

[a] Odds ratio (95% confidence interval) of dropping out of the study

[b] Physician reported

[c] Unknown/undetermined for six children; reference category = generalized

* Statistically significant (p <.05)

Table 7-3. Model fit indices when different numbers of groups were specified.

Number of groups	BIC	Logged Bayes factor [a]	Overall Posterior Probability (Min, Max)	Proportion of patients in each group
2	-5805.41	-	0.956 (0.934, 0.963)	69%, 31%
3	-5802.7	5.42	0.836 (0.758, 0.914)	45%, 34%, 21%
4	-5787.46	30.48	0.818 (0.775, 0.875)	35%, 39%, 19%, 7%
5	-5799.57	-24.22	0.808 (0.792, 0.917)	23%, 44%, 19%, 4%, 10%
6	-5812.24	-25.34	0.781 (0.743, 0.844)	16%, 47%, 15%, 14%, 4%, 3%

[a] Calculated as $2*(BIC_{[complex]} - BIC_{[null]})$; where the more complex model is the one with the greater number of groups. Values ranging from 0 to 2 are interpreted as weak evidence for the more complex model, values ranging from 2 to 6 are interpreted as moderate evidence, values ranging from 6 to 10 are interpreted as strong evidence, and values greater than 10 are interpreted as very strong evidence for the more complex model [30].
BIC: Bayesian information criterion

Table 7-4. Estimates of the trajectory parameters.

Group	Sample size	% Sample	Posterior Probability [a]	OCC [b]	Parameter	β (SE)	p-value
Low-Stable	104	29.2	0.86	12.6	Intercept	5.04 (0.68)	<.0001
					Linear	-0.09 (0.10)	.33
Intermediate-Stable	163	45.8	0.78	5.1	Intercept	11.88 (0.75)	<.0001
					Linear	-0.08 (0.10)	.42
High-Stable	72	20.2	0.88	28.7	Intercept	22.68 (0.72)	<.0001
					Linear	0.13 (0.14)	.37
High-Decreasing	17	4.8	0.85	108.7	Intercept	37.63 (1.88)	<.0001
					Linear	-10.23 (1.67)	<.0001
					Quadratic	0.73 (0.16)	<.0001

[a] Values greater than 0.70 are deemed acceptable and indicative of high assignment accuracy
[b] OCC: Odds of Correct Classification, values greater than 5.0 suggest that the model has high assignment accuracy

Table 7-5. Estimated CES-D score (95% confidence interval) over time for each trajectory group.

Group	At Diagnosis	6 Month Follow-up	1 Year Follow-up	2 Year Follow-up	8 Year Follow-up	10 Year Follow-up
Time [a]	0.00 (0.00)	0.44 (0.09)	0.97 (0.12)	1.98 (0.12)	7.63 (0.79)	10.14 (0.82)
Low-Stable	5.97 (4.36, 7.58)	5.94 (4.38, 7.50)	5.91 (4.40, 7.42)	5.83 (4.41, 7.26)	5.55 (4.10, 7.00)	5.36 (3.64, 7.09)
Intermediate-Stable	12.00 (10.14, 13.85)	11.96 (10.13, 13.80)	11.93 (10.12, 13.74)	11.85 (10.06, 13.64)	11.53 (9.47, 13.60)	11.33 (8.84, 13.81)
High-Stable	22.68 (21.25, 24.10)	22.73 (21.36, 24.10)	22.79 (21.47, 24.11)	22.92 (21.67, 24.17)	23.44 (21.86, 25.01)	23.78 (21.66, 25.89)
High-Decreasing	37.63 (33.90, 41.35)	33.44 (30.55, 36.34)	29.00 (26.44, 31.57)	20.77 (17.16, 24.37)	4.05 (0.00, 10.02)	4.98 (0.00, 11.30)

[a] Mean time (in years) since child's epilepsy diagnosis (standard deviation)

Table 7-6. Baseline characteristics of each trajectory group.

Baseline Characteristics	Group 1 Low-Stable (n = 104)	Group 2 Intermediate-Stable (n = 163)	Group 3 High-Stable (n = 72)	Group 4 High-Decreasing (n = 17)	F/χ2 (p-value)	Contrasts [a]
Child						
Sex, n female	48 (46%)	73 (45%)	39 (54%)	11 (65%)	3.81 (.28)	
Age, years	8 (2.3)	7.9 (2.3)	7.9 (2.6)	8.7 (2.2)	0.70 (.55)	
Focal seizures [b]	53 (51%)	103 (65%)	45 (63%)	11 (65%)	5.12 (.16)	
Epilepsy severity, GASE [b]	5.4 (1.1)	5.4 (1.3)	5.3 (1.1)	5.4 (1.0)	0.44 (.73)	
Comorbidities [b]						
Cognitive	7 (7%)	39 (24%)	20 (28%)	5 (29%)	16.71 (.0008)	2,3,4>1
Behavioral	10 (10%)	26 (16%)	15 (21%)	4 (24%)	5.19 (.16)	
Motor	4 (4%)	12 (7%)	7 (10%)	0 (0%)	(.33) [c]	
At least one of the above	14 (13%)	51 (31%)	28 (39%)	5 (29%)	16.16 (.001)	2,3>1
Seizure free >1 year [d]	67 (88%)	53 (87%)	20 (83%)	2 (67%)	(.52) [c]	
Seizure free >5 years [d]	57 (75%)	38 (62%)	15 (63%)	2 (67%)	(.32) [c]	
Maternal						
Age, years	39.6 (5.1)	38.3 (6.6)	36 (6.1)	35.4 (5.3)	6.23 (.0004)	1>3,4; 2>3
Living with partner	95 (91%)	145 (89%)	59 (82%)	10 (59%)	15.63 (.001)	1,2>4
Works full or part time	71 (68%)	112 (70%)	45 (63%)	8 (47%)	4.02 (.26)	
College/university	73 (70%)	86 (53%)	26 (36%)	5 (29%)	24.39 (<.0001)	1>2; 1,2 >3,4
Family						
Annual Household Income					10.62 (<.0001)	1>2,3,4; 2>4
< $20,000	2 (2%)	10 (6%)	11 (16%)	6 (38%)		
$20,000 - $39,999	9 (9%)	23 (14%)	16 (24%)	2 (13%)		
$40,000 - $59,999	20 (19%)	37 (23%)	13 (19%)	4 (25%)		
$60,000 - $79,999	21 (20%)	31 (20%)	10 (15%)	1 (6%)		
$80,000 - $99,999	17 (16%)	25 (16%)	5 (7%)	2 (13%)		
>$100,000	35 (34%)	33 (21%)	13 (19%)	1 (6%)		
Resources, FIRM	57.8 (8.0)	49.5 (9.1)	43 (11.0)	36.4 (14)	48.00 (<.001)	1>2,3,4; 2>3,4
Demands, FILE	6.7 (5.0)	9.1 (5.8)	12.8 (7.0)	16.5 (9.3)	22.02 (<.0001)	3,4>1,2; 2>1
Functioning, APGAR	16 (2.7)	13.9 (3.4)	12 (3.8)	9.6 (5.2)	29.84 (<.0001)	1>2,3,4; 2>3,4

Mean (Standard Deviation) or n (%) are presented.

[a] Denotes significant (at $p<.05$) pairwise contrasts, e.g. 3>1 indicates that Group 3 is significantly larger (or has higher scores) than Group 1;

[b] Physician reported;

[c] Fishers' exact test;

[d] Provided as a descriptive statistic, is based on the data from the 10-year follow-up visit and therefore was not considered in multivariable regression

Table 7-7. Summary of multinomial regression presenting the odds ratio (OR) and 95% confidence interval (95% CI) for belonging in each trajectory relative to the *Low-Stable* trajectory.

Baseline Characteristics	*p*-value of overall effect	*Intermediate-Stable* OR (95% CI)	*High-Stable* OR (95% CI)	*High-Decreasing* OR (95% CI)
Child				
Focal seizures	.07	**2.19 (1.20, 3.98)** [a]	2.07 (0.93, 4.63)	3.07 (0.77, 12.3)
Cognitive problems	.07	**3.97 (1.39, 11.38)** [a]	**3.99 (1.16, 13.73)** [a]	2.41 (0.34, 17.21)
Behavioural problems	.70	0.58 (0.21, 1.65)	0.55 (0.15, 1.93)	0.36 (0.05, 2.83)
Maternal				
Age	.020	0.96 (0.91, 1.01)	**0.89 (0.83, 0.96)** [b]	0.89 (0.80, 1.01)
College/university education	.21	0.59 (0.32, 1.11)	**0.42 (0.18, 0.96)** [a]	0.45 (0.10, 1.99)
Living with partner	.84	1.30 (0.45, 3.79)	0.92 (0.25, 3.42)	0.72 (0.12, 4.44)
Family				
Household Income	.70	0.93 (0.74, 1.16)	0.95 (0.71, 1.29)	0.75 (0.45, 1.26)
Resources, FIRM [d]	<.0001	**0.93 (0.89, 0.97)** [c]	**0.88 (0.84, 0.93)** [c]	**0.86 (0.79, 0.92)** [c]
Demands, FILE [e]	.27	1.04 (0.98, 1.11)	1.07 (1.00, 1.16)	1.09 (0.98, 1.21)
Functioning, APGAR [f]	.0011	**0.87 (0.78, 0.96)** [c]	**0.79 (0.69, 0.90)** [c]	**0.70 (0.58, 0.85)** [c]

Bolded items highlight statistical significance; [a] $p<.05$; [b] $p<.01$; [c] $p<.001$

[d] Higher scores are indicative of greater of more supportive, organized family environment with few disruptions in daily routines and interactions, and greater extended family social support

[e] Higher scores are indicative of greater family demands and stress

[f] Higher scores are indicative of greater satisfaction with family relationships

Chapter 8: Summary and Discussion

8.1 Introduction

Past research has emphasized the importance and prevalence of psychological comorbidities among children with epilepsy and their parents. In fact, the definition of epilepsy has been updated to include cognitive, psychological, and social consequences as characteristic features of epilepsy [1]. In the long-term, the majority of children (66-80%) achieve seizure-control [2,3], but there has been a lack of research evaluating psychological comorbidities over the long-term for children and their parents. This large gap in our understanding of long-term outcomes, and the characteristics of children and parents likely to show optimal outcomes was evaluated in this thesis research. This chapter summarizes the findings of this thesis research and their implications within the context of the extant literature. Strengths and limitations of this research, as well as suggestions for future research are also discussed.

8.2 Summary of Key Findings

8.2.1 Long-term outcomes for children

Children with newly diagnosed epilepsy were prospectively followed over 10 years to delineate health-related quality of life (HRQOL) trajectories and their determinants. A key finding was that changes in HRQOL observed within the first two years after the diagnosis of epilepsy remained stable over the long-term. We also found that one third of children reported a relatively poor HRQOL at the time of diagnosis, which remained stable and poor throughout the 10-year follow-up. These findings suggest that early interventions may be essential and that how children and their families respond and cope with the illness during the initial period after

diagnosis may be critical and have long-term effects. Severity of epilepsy, neuropsychological comorbidities and family functioning at the time of epilepsy diagnosis were associated with long-term HRQOL trajectories. This finding aligns with the Stress Process Model (Figure 2-1) which suggests that although the clinical characteristics such as severity of illness are important determinants of long-term outcomes, their impact may be mitigated by coping and supportive factors, namely family environment.

8.2.2 Long-term outcomes for mothers

Mothers of children with newly diagnosed epilepsy were prospectively followed over 10 years to delineate their depressive symptom trajectories and their HRQOL at the 10-year follow-up. A key finding was that trajectories of depressive symptoms remained stable over the long-term for the majority of mothers, with 20% scoring in the at-risk range for clinical depression throughout the 10-year follow-up. With respect to HRQOL, the mental health component of mother's HRQOL was similar to that of similarly aged women in the general population. Importantly, we found that neuropsychological comorbidities and family environment at the time of epilepsy diagnosis were significantly associated with long-term trajectories of depressive symptoms in mothers, and that family environment was significantly associated with mothers' HRQOL. Similar to the results reported earlier for children's outcomes, these findings for mothers also align with the Stress Process Model (Figure 2-1) in that coping and supportive factors, namely family environment, are important determinants of mothers' depressive symptoms and HRQOL, and may mitigate the impact of clinical characteristics such as severity of the illness.

8.3 Strengths

This thesis research has several strengths that represent key contributions to the extant literature on children's and parents' outcomes over the long-term after an epilepsy diagnosis. First, data came from a population-based cohort study (HERQULES) of children with newly diagnosed epilepsy recruited across Canada. HERQULES had a strong response rate (82%) and one of the largest samples (n=373) of studies evaluating HRQOL and mental health outcomes among children with epilepsy and their parents. The results of this thesis research can therefore be considered highly generalizable.

Second, the study utilized a prospective design and evaluated outcomes at multiple time points, allowing for the evaluation of long-term trajectories of children's HRQOL and mothers' depressive symptoms. Additionally, the focus on incident cases of epilepsy also allowed for the identification of characteristics, available early in the course of the disorder, that are associated with long-term outcomes. This is essential in delineating the long-term prognosis beyond seizure control and allowing for the early identification of children and parents who are at risk for poor long-term outcomes. The results of this thesis research are the first to prospectively evaluate any aspect of mental health over the long-term for children with epilepsy and their parents and identify baseline factors associated with long-term outcomes.

Third, HERQULES provided a robust and rich data source that evaluated multiple clinical and family characteristics. Importantly, clinical characteristics were reported by the child's treating neurologists, and parents completed multiple measures of parent characteristics and family environment. HERQULES was among the first studies to focus on characteristics beyond seizure control, and allowed for the identification of modifiable factors, namely family environment, that could represent targets of early interventions.

8.4 Limitations

The results of this thesis research should be considered within the context of its limitations. First, although this research is the first to prospectively evaluate long-term mental health outcomes for children with new-onset epilepsy and their parents, attrition was inevitable and primarily occurred because of loss of contact. We retained approximately 72% and 42% of our sample to the 2- and 10-year follow-up, respectively. As mentioned in earlier chapters, however, this research has a distinct advantage since it was possible to include all participants in our prospective analyses of HRQOL and depressive symptoms because latent class growth curve models utilize a likelihood-based technique to predict missing values. In addition, these models explicitly modeled the probability of dropping out to account for non-random attrition. Additionally, we focused on baseline predictors of trajectories that were available for all participants. Nonetheless, given the characteristics of families lost to follow-up, our results may have underestimated the proportion of children with poorer HRQOL trajectories and the proportion of mothers with greater depressive symptoms.

Second, this research was focused on children aged 4-12 years at the time of epilepsy diagnosis, and our results may be not generalizable to children with an earlier age of onset who tend to have more catastrophic types of epilepsy. One reason for choosing the lower age limit was because of the lack of standardized parent-reported HRQOL measures for children younger than four years of age. The inclusion of young children also prevented self-reported HRQOL assessments by children using a mailed survey; parents of young children would most likely have aided their children with questionnaire completion at home and thereby potentially biased their children's report of their HRQOL. Additionally, children younger than eight years of age are thought to lack the cognitive maturity and verbal comprehension skills required to provide

reliable self-reports [4]. Notably, although child self-reports and parent proxy-reports of HRQOL are not considered interchangeable given their unique perspectives and values, parents provide reliable and consistent reports of their children's HRQOL [4,5].

Third, this research was focused on mothers' HRQOL and depressive symptoms and the results are not generalizable to fathers. The primary caregiving parent was asked to complete the questionnaires, with 356 mothers and only 12 fathers completing the survey at multiple times. Given the small sample size of fathers, we focused on mothers to reduce heterogeneity. Additionally, since mothers are most often the primary caregiver of children [6], it is reasonable to assume that mothers may be particularly at risk for distress in response to their children's epilepsy. Lastly, we also did not have data on parents' (and children's) mental health care utilization, which may be associated with trajectories of long-term depressive symptoms. This remains an important area for future investigation.

8.5 Future research and potential implications

As noted above, one limitation of this thesis research was the focus on parents' perceptions of their children's outcomes, primarily as a consequence of the young age of the children and given the data collection strategy of mailed questionnaires. In addressing this limitation, AYA followed in the long-term were asked to complete a self-reported survey at the 8- and 10-year follow-up. The adult (QOLIE-31-P) and adolescent (QOLIE-AD-48) version of a widely utilized epilepsy-specific HRQOL instrument were completed by young adults (aged 18 years or older) and adolescents (aged 11 to 17 years), respectively. A natural next step for future research will be to evaluate AYA's perceptions of their HRQOL in the long-term and compare their reports with that of their parents' proxy-reports. AYA and parents both provide valid,

reliable assessments of AYA's HRQOL, however given their unique perspectives and values their reports are not considered interchangeable [4]. Therefore, it will be important to evaluate long-term HRQOL outcomes as reported by AYA.

The current research was focused on evaluating long-term outcomes and trajectories of children's and parents' HRQOL and mental health. Expanding on these results, a second line of future research should aim to evaluate the moderating and mediating effects of coping and support factors such as family environment, as described in the conceptual framework (Figure 2-1). The HERQULES study is uniquely suited to address this research given that multiple patient, clinical, parent and family characteristics were evaluated at multiple time points over the 10-year follow-up allowing for temporal separation of effects. Indeed, previous work using HERQULES has shown that family stress and satisfaction with family relationships mediate – while family mastery and extended family social support moderate – the negative impact of epilepsy severity and parental psychopathology on children's HRQOL and emotional well-being [7,8]. Expanding this research to include long-term HRQOL and mental health outcomes, will enhance our understanding of the complex interplay between these factors and identify whether family environment has a long-term mediating and moderating effects. Similarly, future research may also evaluate families' responses over time to stress and the epilepsy diagnosis. For example, HERQULES data could be used to calculate changes in scores from diagnosis to the six-month follow-up and the association of any changes observed with the long-term outcomes evaluated here.

Lastly, a third line of future research will be focused on applying the results of this study to inform behavioral interventions. We found that a similar set of clinical, patient, parent, and family characteristics at the time of epilepsy diagnosis were associated with better HRQOL and

mental health outcomes over the long-term for children and their mothers. Specifically, the severity of epilepsy and neuropsychological comorbidities, as well as the family environment at the time of diagnosis were associated with better mental health outcomes. Given that epilepsy severity and its comorbidities are already a focus of clinical care and taken together with the fact that family environment may be modifiable, interventions targeting the family early in the course of the disorder may be effective in improving children's and parents' long-term HRQOL and mental health. Our group has begun implementing these findings by piloting a randomized controlled trial of a mindfulness-based intervention targeting the family unit [9]. The intervention, Making Mindfulness Matter (M3), was modelled after the school-based MindUP program used by over 6 million children in over 12 countries [10-12], and was augmented for provision online and to integrate a parent component. M3 is a concurrent parent and child program delivered over an eight-week period with one 1.5-hour session per week for parents and 1-hour session per week for children. The program is standardised, with parents and children learning the same core principles: how our brains work, stress and the brain, mindful breathing, mindful sensing, mindful movement, perspective taking, optimism, and gratitude/acts of kindness. Within the parent group, the emphasis is on applying the principles and skills directly to parenting. Notably, a key feature of the intervention is its low cost, online group delivery, and facilitation by non-clinician staff which would allow the program to be scalable to communities across Canada and increases its likely sustainability. This ongoing pilot trial is scheduled to end on September 2022 [9].

8.6 Conclusions

Overall, this thesis research makes a significant contribution in delineating the long-term course and factors associated with the health and well-being of children with epilepsy and their parents, and by strengthening the methodological rigour of longitudinal studies for this patient group. This research showed that changes in children's HRQOL early in the course of the disorder are maintained over the long-term and that optimal outcomes may be achieved through interventions delivered early in the course of the disorder. Mothers' course of depressive symptoms remained relatively stable throughout the 10-year follow-up, with 20% of mothers scoring in the at-risk range for clinical depression throughout the follow-up period. Importantly, for both children and their mothers, severity of epilepsy, neuropsychological problems, and family environment at the time of diagnosis were associated with their long-term HRQOL and depressive symptom trajectories. These results are important in providing clinicians, children, and their parents with prognostic information regarding potential long-term outcomes and show that targeting the family environment early on may lead to optimal HRQOL and mental health for children with epilepsy and their parents.

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Appendix A: Data Collection and Measurement

Data used in this dissertation came from the Health-related Quality of Life of Children with Epilepsy Study (HERQULES). HERQULES recruited children aged 4-12 years with newly-diagnosed epilepsy and prospectively followed them over a ten-year period. HERQULES was funded through two independent Canadian Institutes for Health Research (CIHR) grants, one to evaluate the course of children's HRQOL over the short-term (2-year follow-up), and a second to follow the cohort over the long-term (10-year follow-up). The study design, recruitment, and methods used by HERQULES are described below. Ethical approval for HERQULES was obtained from the Research Ethics Board at Western University (REB # 10069E and 102819) and all appropriate ethics boards across the country. Approval forms can be provided upon request.

Recruitment

HERQULES utilized a two-stage clustered sample design, whereby pediatric neurologists were recruited, who were then asked to consecutively recruit their patients meeting inclusion criteria. In the first stage, the membership list of the Canadian Association of Child Neurology (CACN) served as the sampling frame to identify all pediatric neurologists practising across Canada. To ensure completeness, a small group of members from across the country reviewed the list and added the names of a small number of pediatric neurologists who were not on the list and removed members who were not currently practising. A total of 72 eligible pediatric neurologists were identified who were subsequently contacted and agreed to participate. Neurologists were provided with study materials including an overview of the study,

inclusion/exclusion criteria, physicians' questionnaires, study timelines, and a token of appreciation. In the second stage of the clustered sampling design, participating neurologists and their staff approached and recruited eligible parents of children with newly-diagnosed epilepsy. The contact details of eligible and interested parents were sent to the HERQULES staff who facilitated parents' participation in the study (described below). Of the 72 neurologists identified, a total of 53 (74%) were successful in recruiting participants into HERQULES.

Patient recruitment occurred between April 2004 and April 2007. HERQULES staff send letters of information and contacted by phone interested parents to further address any questions and finalize eligibility and participation. The Tailed Design Method was used to maximize participation and response rates; this method outlines a systematic approach for providing reminders, follow-ups, and dissemination of a study newsletter describing the study progress and results in aggregate form. In addition, birthday and holiday cards were sent to patients and their parents. A total of 455 eligible families identified, of whom 373 (82%) participated by completing the baseline questionnaires. Of the 373 participating families, 282 (76%) completed the two-year follow-up, and 173 (46%) completed the 10-year follow-up. A detailed participant flow chart is presented in Figure A-1.

Inclusion and Exclusion Criteria

Study inclusion criteria included: 1) children aged 4 to 12 years, 2) case with newly diagnosed epilepsy (≥2 unprovoked seizures) and seen for the first time by a participating pediatric neurologist, and 3) the parent/caregiver was primarily responsible for the child's care for at least six months and would be continuing for the at least two years (duration of the original study). Additionally, children with newly diagnosed epilepsy but whom had a prior history of

neonatal seizures were included if medication was removed by six weeks of age and seizures did not reoccur. Exclusion criteria included 1) diagnosis of epilepsy was previously confirmed, 2) diagnosis of other progressive or degenerative neurological disorders, or other major comorbid non-neurological health condition likely to have an impact on HRQOL (e.g., asthma requiring daily medication, renal failure), and 3) insufficient English language skills.

Measures and Data Collection

Questionnaires at the time of epilepsy diagnosis and 0.5, 1, 2, 8, and 10 years later were completed by children, parents, and/or neurologists (described below). The time points chosen were based on a priori considerations, as there were no known optimal time points for capturing the variability of HRQOL overtime. Three assessments were completed in the first year on the hypothesis that epilepsy and family factors would be most dynamic during the first-year post-diagnosis. One assessment was chosen during the second year on the hypothesis that family dynamics and epilepsy factors would have become more stable. Lastly, the 8- and 10-year follow-up was chosen to prospectively evaluate long-term outcomes. Each questionnaire is presented in Appendix B.

At the 8- and 10-year follow-up children, who were now adolescents and young adults (AYAs), reported on their HRQOL and seizure-status. Adolescents (aged 11 to 17 years) completed the 48-item Quality of Life in Epilepsy Inventory for Adolescents (QOLIE-AD-48)[1], and young adults (aged 18 years or older) completed the 31-item Patient-Weighted Quality of Life in Epilepsy Questionnaire (QOLIE-31-P)[2]. Patients did not complete questionnaires at earlier time points because there were no epilepsy-specific, self-reported

HRQOL measures available for youth aged 4-12 years appropriate for use in a mailed questionnaire.

Parents completed the questionnaires at the time of epilepsy diagnosis, and 0.5, 1, 2, 8, and 10 years later. Parents reported on their child's HRQOL using the 76-item Quality of Life in Childhood Epilepsy Questionnaire (QOLCE)[3-6], and on their depressive symptoms using the 20-item Center for Epidemiological Studies Depression Scale (CES-D)[7]. Parents also reported on demographic characteristics and completed three standardized measures of family environment: 1) the Family Adaptability, Partnership, Growth, Affection and Resolve (Family APGAR)[8], with higher scores indicative of greater satisfaction with family relations; 2) the Family Inventory of Life Events and Changes (FILE)[9], with higher scores indicative of greater family demands/stressors; and 3) Family Inventory of Resources for Management (FIRM)[10], with higher scores indicative of a more supportive, organized family environment with few disruptions in daily routines and interactions, and greater extended family social support. At the 10-year follow-up parents also reported on their HRQOL using the 12-item Short-Form Health Survey (SF-12v2)[11].

Neurologists completed a one-page questionnaire at the time of epilepsy diagnosis, and 0.5, 1, 2, 8, and 10 years later. Neurologists reported on clinical characteristics and on the child's epilepsy severity using the single item Global Assessment of Severity of Epilepsy scale (GASE)[12,13]. Neurologist's reports of the type of epilepsy syndrome were coded in two ways, broadly (focal vs. generalized) and by specific subtype (generalized, absence, focal, benign epilepsy of childhood with rolandic spikes (BECRS), focal to bilateral tonic-clonic, BECRS + focal to bilateral tonic-clonic, and undetermined). Neurologists' reports at the 8- and 10-year

follow-up were limited because majority of AYAs (72%) had not received epilepsy-related care in the year preceding the last follow-up.

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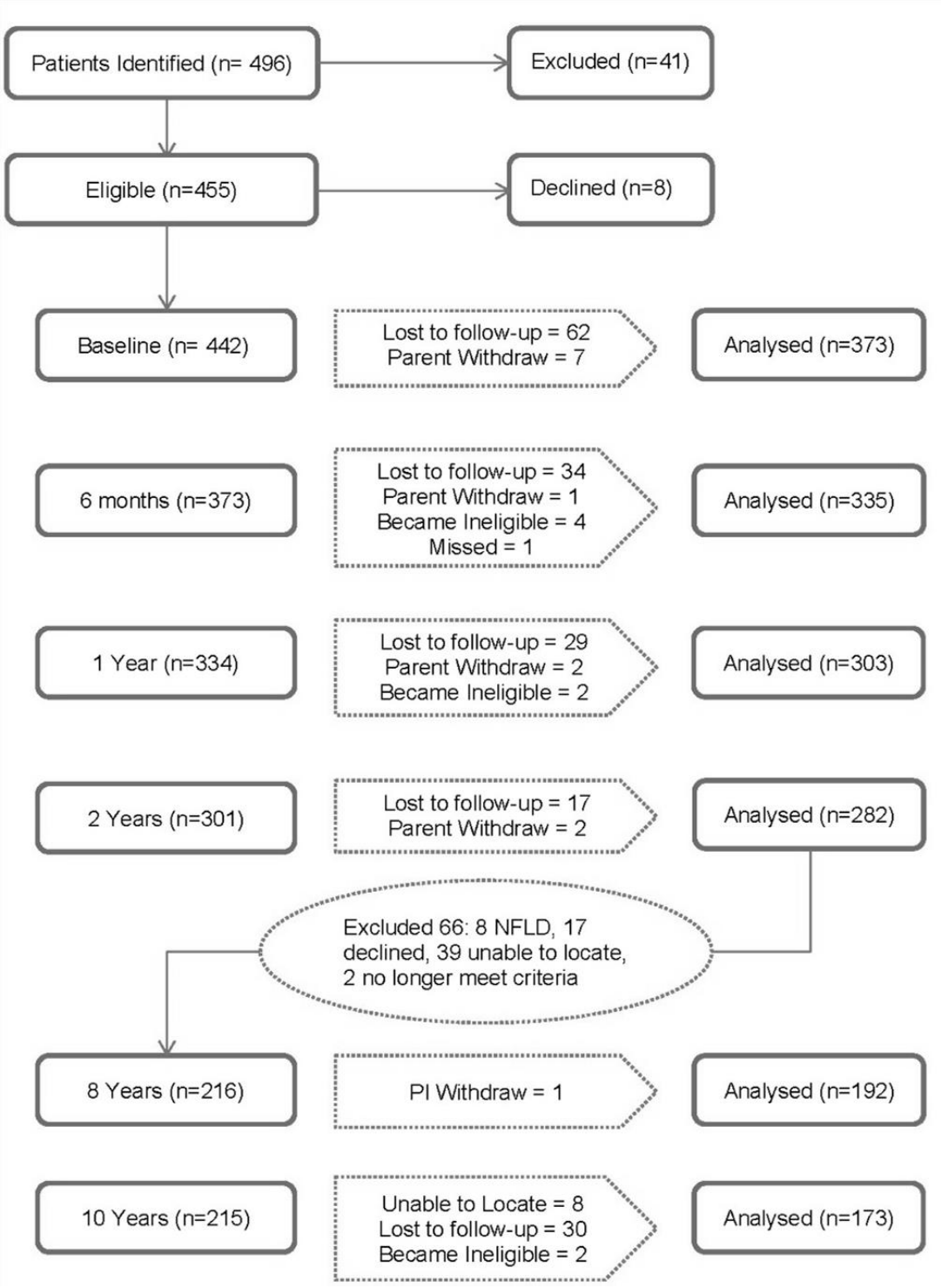
Figure A-1. Detailed participant flow chart.



Appendix B: Questionnaires Used in Dissertation

Quality of Life in Childhood Epilepsy Questionnaire (QOLCE; 76-item)

YOUR CHILD'S PHYSICAL ACTIVITIES

The following questions ask about physical activities your child might do.

1.1. In his/her daily activities during the past 4 weeks, how often has your child:

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not applicable
a. needed more supervision than other children his/her age?	☐	☐	☐	☐	☐	☐
b. needed special precautions (i.e. wearing a helmet)?	☐	☐	☐	☐	☐	☐
c. played freely in the house like other children his/her age?	☐	☐	☐	☐	☐	☐
d. played freely outside the house like other children his/her age?	☐	☐	☐	☐	☐	☐
e. gone swimming? (i.e. swam independently)	☐	☐	☐	☐	☐	☐
f. participated in sports activities (other than swimming)?	☐	☐	☐	☐	☐	☐
g. stayed out overnight (with friends or family)?	☐	☐	☐	☐	☐	☐
h. played with friends away from you or your home?	☐	☐	☐	☐	☐	☐
i. gone to parties without you or without supervision?	☐	☐	☐	☐	☐	☐
j. been able to do the physical activities other children his/her age do?	☐	☐	☐	☐	☐	☐

1.2. During the past 4 weeks, how much of the time do you think your child:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	Not applicable
a. felt tired	☐	☐	☐	☐	☐	☐
b. felt energetic	☐	☐	☐	☐	☐	☐

1.3. Is there anything else you would like to tell us about your child's activities?

WELL-BEING

Below is a list that describes how your child might feel in general.

1.4. During the past 4 weeks, how much of the time do you think your child:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	Not applicable
a. felt down or depressed?	☐	☐	☐	☐	☐	☐
b. felt calm?	☐	☐	☐	☐	☐	☐
c. felt helpless in situations?	☐	☐	☐	☐	☐	☐
d. felt happy?	☐	☐	☐	☐	☐	☐
e. wished s/he was dead?	☐	☐	☐	☐	☐	☐
f. felt in control?	☐	☐	☐	☐	☐	☐
g. felt tense and anxious?	☐	☐	☐	☐	☐	☐
h. felt frustrated?	☐	☐	☐	☐	☐	☐
i. felt overwhelmed by events?	☐	☐	☐	☐	☐	☐
j. worried a lot?	☐	☐	☐	☐	☐	☐
k. felt confident?	☐	☐	☐	☐	☐	☐
l. felt excited or interested in something?	☐	☐	☐	☐	☐	☐
m. felt pleased about achieving something?	☐	☐	☐	☐	☐	☐
n. got easily embarrassed?	☐	☐	☐	☐	☐	☐
o. felt different or singled out?	☐	☐	☐	☐	☐	☐
p. felt nobody understood him/her?	☐	☐	☐	☐	☐	☐
q. felt valued?	☐	☐	☐	☐	☐	☐
r. felt s/he was not good at anything?	☐	☐	☐	☐	☐	☐
s. felt no one cared?	☐	☐	☐	☐	☐	☐

1.5. Is there anything else you would like to tell us about how your child feels in general?

COGNITION

The following questions ask about some problems children have with concentrating, remembering, and speaking.

1.6. Compared to other children of his/her own age, how often during the past 4 weeks has your child:

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not applicable
a. had difficulty attending to an activity?	☐	☐	☐	☐	☐	☐
b. had difficulty reasoning or solving problems?	☐	☐	☐	☐	☐	☐
c. had difficulty making plans or decisions?	☐	☐	☐	☐	☐	☐
d. had difficulty keeping track of conversations?	☐	☐	☐	☐	☐	☐
e. had trouble concentrating on a task?	☐	☐	☐	☐	☐	☐
f. had difficulty concentrating on reading?	☐	☐	☐	☐	☐	☐
g. had difficulty doing one thing at a time?	☐	☐	☐	☐	☐	☐
h. reacted slowly to things being said & done?	☐	☐	☐	☐	☐	☐
i. completed activities that needed organising/planning?	☐	☐	☐	☐	☐	☐
j. found it hard remembering things?	☐	☐	☐	☐	☐	☐
k. had trouble remembering names of people?	☐	☐	☐	☐	☐	☐
l. had trouble remembering where s/he put things?	☐	☐	☐	☐	☐	☐
m. had trouble remembering things people told him/her?	☐	☐	☐	☐	☐	☐
n. had trouble remembering things s/he read hours or days before?	☐	☐	☐	☐	☐	☐
o. planned to do something then forgot?	☐	☐	☐	☐	☐	☐
p. had trouble finding the correct words?	☐	☐	☐	☐	☐	☐
q. had trouble understanding or following what others were saying?	☐	☐	☐	☐	☐	☐
r. had trouble understanding directions?	☐	☐	☐	☐	☐	☐
s. had difficulty following simple instructions?	☐	☐	☐	☐	☐	☐
t. had difficulty following complex instructions?	☐	☐	☐	☐	☐	☐
u. had trouble understanding what s/he read?	☐	☐	☐	☐	☐	☐
v. had trouble writing?	☐	☐	☐	☐	☐	☐
w. had trouble talking?	☐	☐	☐	☐	☐	☐

1.7. Is there anything else you would like to tell us about your child's concentration, memory or speech?

YOUR CHILD'S SOCIAL ACTIVITIES

1.8. During the past 4 weeks, how often has your child's epilepsy:

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not applicable
a. limited his/her social activities (visiting friends, close relatives, or neighbours)?	☐	☐	☐	☐	☐	☐
b. helped him/her to make friends?	☐	☐	☐	☐	☐	☐
c. affected his/her social interactions at school or work?	☐	☐	☐	☐	☐	☐
d. improved his/her friendships & relationships with others?	☐	☐	☐	☐	☐	☐
e. limited his/her leisure activities (hobbies or interests)?	☐	☐	☐	☐	☐	☐
f. isolated him/her from others?	☐	☐	☐	☐	☐	☐
g. improved his/her relations with family members?	☐	☐	☐	☐	☐	☐
h. made it difficult for him/her to keep friends?	☐	☐	☐	☐	☐	☐
i. frightened other people?	☐	☐	☐	☐	☐	☐

1.9. During the past 4 weeks, how limited are your child's social activities compared with others his/her age because of his/her epilepsy or epilepsy-related problems?

☐ Yes, limited a lot ☐ Yes, limited some ☐ Yes, limited a little ☐ Yes, but rarely ☐ No, not limited

1.10. During the past 4 weeks, how often has your child freely discussed his/her epilepsy with friends?

☐ Very often ☐ Fairly often ☐ Sometimes ☐ Almost Never ☐ Not applicable

1.11. During the past 4 weeks, how often has your child freely discussed his/her epilepsy with family?

☐ Very often ☐ Fairly often ☐ Sometimes ☐ Almost Never ☐ Not applicable

1.12. Is there anything else you would like to tell us about your child's social activities?

YOUR CHILD'S BEHAVIOUR

Below are statements that describe some children's behaviour.
Please try to answer all questions as well as you can, even if some do not seem to apply to your child.

1.13. Compared to other children his/her own age, how often during the past 4 weeks do each of the following statements describe your child?

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not applicable
a. relied on you/family to do things for him/her that s/he was able to do him/herself	☐	☐	☐	☐	☐	☐
b. asked for reassurance	☐	☐	☐	☐	☐	☐
c. was socially inappropriate (said or did something out of place in a social situation)	☐	☐	☐	☐	☐	☐
d. wanted things to be perfect	☐	☐	☐	☐	☐	☐
e. did not give up easily	☐	☐	☐	☐	☐	☐
f. angered easily	☐	☐	☐	☐	☐	☐
g. hit or attacked people	☐	☐	☐	☐	☐	☐
h. swore in public	☐	☐	☐	☐	☐	☐
i. joined in activities with other children	☐	☐	☐	☐	☐	☐
j. feared unfamiliar places, situations or people	☐	☐	☐	☐	☐	☐
k. preferred his/her own company instead of seeking out others	☐	☐	☐	☐	☐	☐
l. was obedient	☐	☐	☐	☐	☐	☐
m. set high standards for self	☐	☐	☐	☐	☐	☐
n. did not worry about what others thought	☐	☐	☐	☐	☐	☐
o. get along with other children	☐	☐	☐	☐	☐	☐
p. wished s/he was someone or somewhere else	☐	☐	☐	☐	☐	☐
q. acted without thinking	☐	☐	☐	☐	☐	☐
r. demanded a lot of attention	☐	☐	☐	☐	☐	☐

Compared to other children his/her own age, how often during the past 4 weeks do each of the following statements describe your child?

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not applicable
s. was decisive	☐	☐	☐	☐	☐	☐
t. was independent	☐	☐	☐	☐	☐	☐
u. preferred routines or disliked changes	☐	☐	☐	☐	☐	☐
v. did things just to prove s/he could	☐	☐	☐	☐	☐	☐
w. preferred the company of adults	☐	☐	☐	☐	☐	☐

1.14. Is there anything else you would like to tell us about your child's behaviour?

GENERAL HEALTH

1.15. Compared to other children his/her age, how do you think your child's health has been in the past 4 weeks? Please consider your child's epilepsy as part of his/her health when you answer this question.

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

1.16. Is there anything else you would like to tell us about how epilepsy has affected your child's health?

QUALITY OF LIFE

1.17. In the past 4 weeks what has your child's quality of life been?

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

1.18. Consider your child's present skills in thinking, learning, remembering, speaking and understanding. Taken together, do you think that your child is functioning:

- ☐ At the level expected for his/her age?
- ☐ Somewhat behind the level expected for his/her age?
- ☐ Significantly behind the level expected for his/her age?

Quality of Life in Epilepsy for Adolescents (QOLIE-48 AD)

1. In general, would you say your health is: ***(Circle one number)***

Excellent	Very Good	Good	Fair	Poor
5	4	3	2	1

2. **Compared to 1 year ago,** how would you rate your health in general **now**?

Much better now	Somewhat better now	About the same now	Somewhat worse now	Much worse now
5	4	3	2	1

The following questions are about activities you might do during a TYPICAL DAY. We want you to answer how much **your health** limits you in these activities.

(Circle one number on each line)

In the past 4 weeks, how often has your health limited:	Very often	Often	Some-times	Not often	Never
3. Heavy activities, such as running, participating in very active sports (such as gymnastics, roller-blading, skiing)?	1	2	3	4	5
4. Moderate activities (such as walking to school, bicycle riding)?	1	2	3	4	5
5. Light activities (such as carrying packages or a school bag full of books)?	1	2	3	4	5
6. Other daily activities (such as taking a bath/shower alone, going to and from school alone)?	1	2	3	4	5

The following questions are about your regular daily activities, such as chores at home, baby-sitting, attending school, being with friends and family, doing homework, or taking part in after-school activities and lessons. We want to know if you had any of the following difficulties with your regular activities as a result of any **physical problems (such as illness) or emotional problems (such as feeling sad or nervous)?**

(Circle one number on each line)

In the past 4 weeks, how have physical or emotional problems caused you to:	Very often	Often	Some-times	Not often	Never
7. Do fewer things than you would have liked to	1	2	3	4	5
8. Limited the ***kind*** of schoolwork, chores, sports, or other activities you did?	1	2	3	4	5
9. Have ***difficulty*** performing the schoolwork, chores, sports, or other activities you did (for example, it took extra effort)?	1	2	3	4	5

In the past 4 weeks, how often:	Very often	Often	Some-times	Not often	Never
10. Did you skip school for no reason	1	2	3	4	5
11. Were you in trouble in school (with teachers or other staff)?	1	2	3	4	5
12. Were you in trouble out of school (with police, security guards, bus driver, etc)?	1	2	3	4	5

These questions are about how you FEEL and how things have been for you during **the past 4 weeks**. For each question, please indicate the one answer that comes closest to the way you have been feeling.

(Circle one number on each line)

In the past 4 weeks, how often have you:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
13. Had trouble concentrating on an activity?	1	2	3	4	5
14. Had trouble concentrating on reading?	1	2	3	4	5

The following questions are about mental activities and language problems that may interfere with your normal schoolwork or living activities. ***(Circle one number on each line)***

In the past 4 weeks, how often have you:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
15. Had difficulty thinking	1	2	3	4	5
16. Had difficulty figuring out and solving problems (such as making plans, making decisions, learning new things)?	1	2	3	4	5
17. Had a problem with complicated projects that require organization or planning like computer games or difficult homework?	1	2	3	4	5
18. Had trouble remembering things you read hours or days before?	1	2	3	4	5
19. Had trouble finding the correct word?	1	2	3	4	5
20. Had trouble understanding your teachers?	1	2	3	4	5
21. Had trouble understanding what you read?	1	2	3	4	5

The following questions ask about the support you get from others (including family and friends).

In the past 4 weeks, how often did you:	*(Circle one number on each line)* Very often	Often	Some-times	Not often	Never
22. Have someone available to help you if you needed and wanted help?	5	4	3	2	1
23. Have someone you could confide in or talk to about things that were troubling you?	5	4	3	2	1
24. Have someone you could talk to when you were confused and needed to sort things out?	5	4	3	2	1
25. Have someone who accepted you as you were, both your good points and bad points?	5	4	3	2	1

The following questions ask about how your epilepsy or medications (antiepileptic drugs) have affected your life in the past 4 weeks.

In the past 4 weeks, how often did you:	*(Circle one number on each line)* Very often	Often	Some-times	Not often	Never
26. Feel that **epilepsy or medications** limited your social activities (such as hanging out with friends, doing extra-curricular activities) compared with social activities of others your age?	1	2	3	4	5
27. Feel alone and isolated from others because of your epilepsy/seizures?	1	2	3	4	5
28. Miss classes because of seizures or medications?	1	2	3	4	5

In the past 4 weeks, how often did you:	Very often	Often	Some-times	Not often	Never
29. Use epilepsy or medication side effects as an excuse to avoid doing something you didn't really want to do?	1	2	3	4	5
30. Feel embarrassed or "different" because you had to take medications?	1	2	3	4	5
31. Feel that epilepsy or medications limited your school performance?	1	2	3	4	5
32. Feel you had limitations because of your seizures	1	2	3	4	5
33. Feel that epilepsy or medications limited your independence?	1	2	3	4	5
34. Feel that epilepsy or medications limited your social life or dating?	1	2	3	4	5
35. Feel that epilepsy or medications limited your participation in sports or physical activities?	1	2	3	4	5

The following question asks about possible side effects from antiepileptic drugs.

In the past 4 weeks, how did you feel:	Very Bad	Bad	OK	Good	Very Good
36. About how you looked (side effects such as weight gain, acne/pimples, hair change, etc.)?	1	2	3	4	5

In the past 4 weeks, how much were you bothered by:	A Lot	Some	Not Much	A Little	Not at All
37. Limits set by parents/family because of your epilepsy or medications?	1	2	3	4	5

Next are some statements people with epilepsy sometimes make about themselves. For each statement, circle the answer that comes closest to the way **you** have felt about **yourself** in the **past 4 weeks**.

	Strongly agree	Agree	Disagree	Strongly disagree
38. I consider myself to be less than perfect because I have epilepsy.	1	2	3	4
39. If I applied for a job, and someone else also applied who didn't have epilepsy, the employer should hire the other person.	1	2	3	4
40. I can understand why someone wouldn't want to date me because I have epilepsy.	1	2	3	4
41. I don't blame people for being afraid of me because I have epilepsy.	1	2	3	4
42. I don't blame people for taking my opinions less seriously than they would if I didn't have epilepsy.	1	2	3	4
43. I feel that my epilepsy makes me mentally unstable.	1	2	3	4

The following questions ask about your attitudes toward epilepsy. ***Circle one number*** for how often in the **past 4 weeks** you have had these attitudes.

	Very bad	A little bad	Not sure	A little good	Very good
44. How good or bad has it been that you have epilepsy?	1	2	3	4	5
	Very unfair	A little unfair	Not sure	A little fair	Very fair
45. How fair has it been that you have epilepsy?	1	2	3	4	5
	Very sad	A little sad	Not sure	A little happy	Very happy
46. How happy or sad has it been for you to have epilepsy?	1	2	3	4	5

	Very bad	A little bad	Not sure	A little good	Very good
47. How good or bad have you felt it is to have epilepsy?	1	2	3	4	5

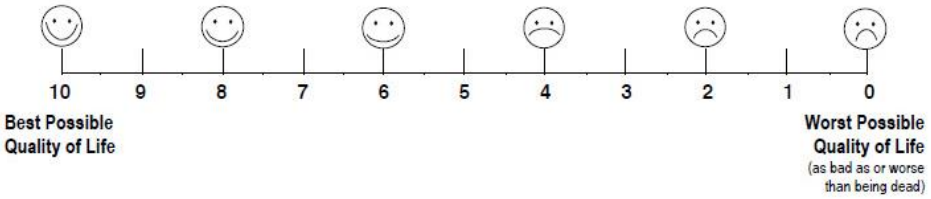
	Very often	Often	Some-times	Not often	Never
48. How often do you feel that your epilepsy kept you from starting new things?	1	2	3	4	5

Optional Items:

In the past 4 weeks, how often did you:	Very often	Often	Some-times	Not often	Never
49. Worry about having another seizure?	1	2	3	4	5
50. Fear dying because of seizures?	1	2	3	4	5
51. Worry about hurting yourself during a seizure?	1	2	3	4	5

Patient Weighted Quality Of Life In Epilepsy (QOLIE-31P)

1. Overall, how would you rate your quality of life?
(*Circle one number on the scale below*)



3

Part A.

These questions are about how you have been FEELING during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks....
(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
2. Did you feel full of pep?	**1**	**2**	**3**	**4**	**5**	**6**
3. Did you have a lot of energy?	**1**	**2**	**3**	**4**	**5**	**6**
4. Did you feel worn out?	**1**	**2**	**3**	**4**	**5**	**6**
5. Did you feel tired?	**1**	**2**	**3**	**4**	**5**	**6**

*Reviewing only questions in **Part A**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
6. How much do the above problems and worries about energy **distress** you overall?	**1**	**2**	**3**	**4**	**5**

4

Part B.

These questions are about how you have been FEELING during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks....
(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
7. Have you been a very nervous person?	**1**	**2**	**3**	**4**	**5**	**6**
8. Have you felt so down in the dumps that nothing could cheer you up?	**1**	**2**	**3**	**4**	**5**	**6**
9. Have you felt clam and peaceful?	**1**	**2**	**3**	**4**	**5**	**6**
10. Have you felt downhearted and blue?	**1**	**2**	**3**	**4**	**5**	**6**
11. Have you been a happy person?	**1**	**2**	**3**	**4**	**5**	**6**

*Reviewing only questions in **Part B**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
12. How much do the above problems and worries about <u>emotions</u> **distress** you overall?	**1**	**2**	**3**	**4**	**5**

5

Part C.

These questions are about how you FEEL and about problems you may have with daily ACTIVITIES during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

The following question asks about how you FEEL and how things have been going for you.

How much of the time during the past 4 weeks....
(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
13. Has your health limited your social activities (such as visiting with friends or close relatives)?	**1**	**2**	**3**	**4**	**5**	**6**

The following questions ask about problems you may have with certain ACTIVITIES.

How much of the time during the past 4 weeks your epilepsy or antiepileptic medication has caused trouble with....

(Circle one number on each line)

	A great deal	A lot	Somewhat	Only a little	Not at all
14. Leisure activities (such as hobbies, going out)	**1**	**2**	**3**	**4**	**5**
15. Driving (or transportation)	**1**	**2**	**3**	**4**	**5**

	Not at all bothersome				Extremely bothersome
16. How much do your work limitations bother you?	**1**	**2**	**3**	**4**	**5**
17. How much do your social limitations bother you?	**1**	**2**	**3**	**4**	**5**

*Reviewing only questions in **Part C**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
18. How much do the above problems and worries about daily activities **distress** you overall?	**1**	**2**	**3**	**4**	**5**

Part D.

These questions are about thinking, reading, concentrating, and memory problems you may have had during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks....

(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
19. Did you have difficulty reasoning and solving problems (such as making plans, making decisions, learning new things)?	**1**	**2**	**3**	**4**	**5**	**6**

	Yes, a great deal	Yes, somewhat	Only A little	No, not at all
20. In the past 4 weeks, have you had any trouble with your memory?	**1**	**2**	**3**	**4**

In the past 4 weeks, how often have you had...
(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
21. Trouble remembering things people tell you?	**1**	**2**	**3**	**4**	**5**	**6**
22. Trouble concentrating on reading	**1**	**2**	**3**	**4**	**5**	**6**
23. Trouble concentrating on doing one thing at a time?	**1**	**2**	**3**	**4**	**5**	**6**

	Not at all bothersome				Extremely bothersome
24. How much do your memory difficulties bother you?	**1**	**2**	**3**	**4**	**5**

*Reviewing only questions in **Part D**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
25. How much do the above problems and worries about <u>mental function</u> **distress** you overall?	**1**	**2**	**3**	**4**	**5**

8

Part E.

These questions are about problems you may have related to your epilepsy or antiepileptic medication.

During the past 4 weeks...

(Circle one number on each line)

	Not at all bothersome				Extremely bothersome
26. How much do physical effects of antiepileptic medication bother you?	**1**	**2**	**3**	**4**	**5**
27. How much do mental effects of antiepileptic medication bother you?	**1**	**2**	**3**	**4**	**5**

	Very worried	Somewhat worried	Not very worried	Not worried at all
28. How worried are you that medications you are taking will be bad for you if taken for a long time?	**1**	**2**	**3**	**4**

*Reviewing only questions in **Part E**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
29. How much do the above problems and worries about <u>effects of medication</u> **distress** you overall?	**1**	**2**	**3**	**4**	**5**

9

Part F.

These questions are about how you FEEL about your seizures during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks....
(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
30. Have you worried about having another seizure?	**1**	**2**	**3**	**4**	**5**	**6**

	Very fearful	Somewhat fearful	Not very fearful	Not fearful at all
31. How fearful are you of having a seizure during the next month?	**1**	**2**	**3**	**4**

	Worry a lot	Occasionally worry	Don't worry at all
32. Do you worry about hurting yourself during a seizure?	**1**	**2**	**3**

	Very worried	Somewhat worried	Not very worried	Not worried at all
33. How worried are you about embarrassment or other social problems resulting from having a seizure during the next month?	**1**	**2**	**3**	**4**

	Not at all bothersome				Extremely bothersome
34. How much do your seizures bother you?	**1**	**2**	**3**	**4**	**5**

10

*Reviewing only questions in **Part F**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

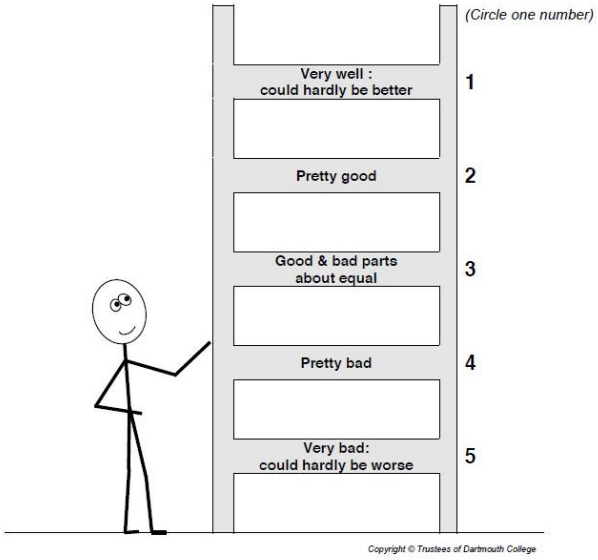
(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
35. How much do the above problems and worries about seizures **distress** you overall?	**1**	**2**	**3**	**4**	**5**

Part G.

The following question asks about how you FEEL about your overall quality of life. Please indicate the one answer that comes closest to the way you have been feeling.

36. How was the **QUALITY OF YOUR LIFE** been during the **past 4 weeks** (that is, how have things been going for you)?



*Reviewing only questions 1 and 36 in **Part G** (on page 1 and this page), consider the overall impact of your quality of life **in the past 4 weeks.***

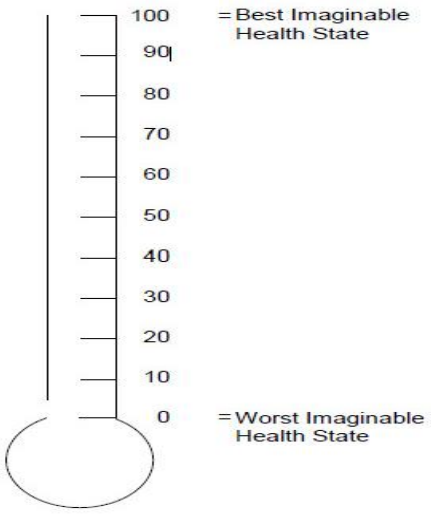
(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
37. How much does the state of your quality of life **distress** you overall?	**1**	**2**	**3**	**4**	**5**

Part H.

38. How good or bad do you think your HEALTH is?

On the scale below, the best imaginable state of health is 100 and the worst imaginable state is zero (0). Please indicate how you feel about your health by circling one number on the scale. **Please consider your epilepsy as part of your health when you answer this question.**



Part I.

*Consider **ALL** the questions you have answered, please **indicate the areas** related to your epilepsy that are most **IMPORTANT** to you **NOW**.*

39. *Number the following topics from '1' to '7', with '1' corresponding to the very most important topic and '7' to the least important one. Please use each number only once.*

|___| **A.** Energy (tiredness)

|___| **B.** Emotions (mood)

|___| **C.** Daily activities (work, driving, social)

|___| **D.** Mental activity (thinking, concentration, memory)

|___| **E.** Medication effects (physical, mental)

|___| **F.** Seizure worry (impact of seizures)

|___| **G.** Overall quality of life

Short Form Health Survey (SF-12v2)

This next set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. If you are unsure about how to answer a question, please give the best answer you can.

3.3. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

3.4. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
b. Climbing several flights of stairs	☐	☐	☐

3.5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐	☐	☐	☐	☐
b. Were limited in the kind of work or other activities	☐	☐	☐	☐	☐

3.6. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐	☐	☐	☐	☐
b. Did work or other activities less carefully than usual	☐	☐	☐	☐	☐

3.7. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

3.8. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	☐	☐	☐	☐	☐
b. Did you have a lot of energy?	☐	☐	☐	☐	☐
c. Have you felt downhearted and depressed?	☐	☐	☐	☐	☐

3.9. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

Center for Epidemiologic Studies Depression Scale (CES-D)

6.1. Now we'd like to ask some questions about you. Please read these sentences that say something about how people sometimes feel and circle the number of the category on this page that best indicates how often you have felt this way in the past 7 days.

0. Rarely or none of the time (less than one day)
1. Some or a little of the time (1-2 days)
2. Occasionally or a moderate amount of time (3-4 days)
3. Most or all of the time (5-7 days)

During the past seven days:

a)	I was bothered by things that usually don't bother me.	0	1	2	3
b)	I did not feel like eating; my appetite was poor.	0	1	2	3
c)	I felt that I could not shake off the blues even with help from my family or friends.	0	1	2	3
d)	I felt that I was just as good as other people.	0	1	2	3
e)	I had trouble keeping my mind on what I was doing.	0	1	2	3
f)	I felt depressed.	0	1	2	3
g)	I felt that everything I did was an effort.	0	1	2	3
h)	I felt hopeful about the future.	0	1	2	3
i)	I thought my life had been a failure.	0	1	2	3
j)	I felt fearful.	0	1	2	3
k)	My sleep was restless.	0	1	2	3
l)	I was happy.	0	1	2	3
m)	I talked less than usual.	0	1	2	3
n)	I felt lonely.	0	1	2	3
o)	People were unfriendly.	0	1	2	3
p)	I enjoyed life.	0	1	2	3
q)	I had crying spells.	0	1	2	3
r)	I felt sad.	0	1	2	3
s)	I felt that people dislike me.	0	1	2	3
t)	I could not get "going".	0	1	2	3

Family Inventory of Resources for Management (FIRM)

3.1. The next set of questions asks about what social, psychological, community and financial resources families believe they have available to them in the management of family life. To complete this inventory you are asked to read the list of "Family Statements" one at a time. In each statement, "family" means your immediate family (mother and/or father and children.) Then ask yourself: *"How well does the statement describe our family situation?"*

Then make your decision by circling one of the following:

0 = Not At All This statement does not describe our family situation. This does not happen in our family.
1 = Minimally This statement describes our family situation only slightly. Our family may be like this once in a while.
2 = Moderately This statement describes our family situation fairly well. Our family is like this some of the time.
3 = Very Well This statement describes our family very accurately. Our family is like this most of the time.

Please read and record your decision for each of the statements below.

Family Statements:	**Not at all**	**Minimally**	**Moderately**	**Very Well**
a. Being physically tired much of the time is a problem in our family	0	1	2	3
b. We have to nag each other to get things done	0	1	2	3
c. We do not plan too far ahead because many things turn out to be a matter of good or bad luck anyway	0	1	2	3
d. Having only one person in the family earning money is (or would be) a problem in our family	0	1	2	3
e. It seems that members of our family take each other for granted	0	1	2	3
f. Sometimes we feel we don't have enough control over the direction our lives are taking	0	1	2	3
g. Certain members of our family do all the giving, while others do all the taking	0	1	2	3
h. We seem to put off making decisions	0	1	2	3
i. Our family is under a lot of emotional stress	0	1	2	3
j. Many things seem to interfere with family members being able to share concerns	0	1	2	3
k. Most of the money decisions are made by only one person in our family	0	1	2	3
l. It seems that we have more illness (colds, flu, etc.) in our family than other people do	0	1	2	3
m. In our family some members have many responsibilities while others don't have enough	0	1	2	3
n. It is upsetting to our family when things don't work out as planned	0	1	2	3
o. Being sad or "down" is a problem in our family	0	1	2	3
p. It is hard to get family members to cooperate with each other	0	1	2	3
q. Many times we feel we have little influence over the things that happen to us	0	1	2	3
r. We have the same problems over and over – we don't seem to learn from past mistakes	0	1	2	3
s. There are things at home we need to do that we don't seem to get done	0	1	2	3
t. We seem to be so involved with work and/or school activities that we don't spend enough time together as a family	0	1	2	3
u. Our relatives seem to take from us, but give little in return	0	1	2	3
v. We try to keep in touch with our relatives as much as possible	0	1	2	3
w. Our relative(s) are willing to listen to your problems	0	1	2	3
x. Our relatives do and say things that make us feel appreciated	0	1	2	3

Family Inventory of Life Events & Changes (FILE)

4.1. Over their life cycle, all families experience many changes as a result of normal growth and development of members and due to external circumstances. The following list of family life changes can happen in a family at any time. Because family members are connected to each other in some way, a life change for any one member affects all the other persons in the family to some degree.

"***FAMILY***" *means a group of two or more persons living together who are related by blood, marriage or adoption. This includes persons who live with you and to whom you have a long term commitment.*

Please read each family life change and decide whether it happened to any member of your family - **including you** - during the past 12 months and check **Yes** or **No**.

Did the change happen in your family:	During the Last 12 Months		
	Yes	**No**	**Score**
I. Intrafamily Strains			
a. Increase of husband/father's time away from family			46
b. Increase of wife/mother's time away from family			51
c. A member appears to have emotional problems			58
d. A member appears to depend on alcohol or drugs			66
e. Increase in conflict between husband and wife			53
f. Increase in arguments between parent(s) and child(ren)			45
g. Increase in conflict among children in the family			48
h. Increased difficulty in managing teenage child(ren)			55
i. Increased difficulty in managing school age child(ren) (6-12 yrs)			39
j. Increased difficulty in managing preschool age child(ren) (2.5-6 yrs)			36
k. Increased difficulty in managing toddler(s) (1-2.5 yrs)			36
l. Increased difficulty in managing infant(s) (0-1 yr)			35
m. Increase in the amount of "outside activities" which the children are involved in			25
n. Increased disagreement about a member's friends or activities			35

Did the change happen in your family:	During the Last 12 Months **Yes**	**No**	**Score**
o. Increase in the number of problems or issues which don't get resolved			45
p. Increase in the number of tasks or chores which don't get done			35
q. Increased conflict with in-laws or relatives			40
II. Marital Strains			
a. Spouse/parent was separated or divorced			79
b. Spouse/parent had an "affair"			68
c. Increased difficulty in resolving issues with a "former" or separated spouse			47
d. Increased difficulty with sexual relationship between husband and wife			58
III. Pregnancy and Childbearing Strains			
a. Spouse had unwanted or difficulty pregnancy			45
b. An unmarried member became pregnant			65
c. A member had an abortion			50
d. A member gave birth to or adopted a child			50
IV. Finance and Business Strains			
a. Took out a loan or refinanced a loan to cover increased expenses			29
b. Went on welfare			55
c. Change in conditions (economic, political, weather) which hurts the family investments			41
d. Change in agriculture market, stock market, or land values which hurts family investments and/or income			43
e. A member started a new business			50
f. Purchased or built a home			41
g. A member purchased a car or other major item			19
h. Increased financial debts due to over-use of credit cards			31
i. Increased strain on family "money" for medical/dental expenses			23
j. Increased strain on family "money" for food, clothing, energy, home care			21
k. Increased strain on family "money" for child(ren)'s education			22
l. Delay in receiving child support or alimony payments			41
V. Work-Family Transitions and Strains			
a. A member changed to a new job/career			40
b. A member lost or quit a job			55
c. A member retired from work			48
d. A member started or returned to work			41
e. A member stopped working for extended period (e.g., laid off, leave of absence, strike)			51
f. Decrease in satisfaction with job/career			45
g. A member had increased difficulty with people at work			32
h. A member was promoted at work or given more responsibilities			40
i. Family moved to a new home/apartment			43

Did the change happen in your family:	During the Last 12 Months		
	Yes	**No**	**Score**
j. A child/adolescent member changed to a new school			24
VI. Illness and Family "Care" Strains			
a. Parent/spouse became seriously ill or injured			44
b. Child became seriously ill or injured			35
c. Close relative or friend of the family became seriously ill			44
d. A member became physically disabled or chronically ill			73
e. Increased difficulty in managing a chronically ill or disabled member			58
f. Member or close relative was committed to an institution or nursing home			44
g. Increased responsibility to provide direct care or financial help to husband's and/or wife's parents			47
h. Experienced difficulty in arranging for satisfactory child care			40
VII. Losses			
a. A parent/spouse died			98
b. A child member died			99
c. Death of husband's or wife's parent or close relative			48
d. Close friend of the family died			47
e. Married son or daughter was separated or divorced			58
f. A member "broke up" a relationship with a close friend			35
VIII. Transitions "In and Out"			
a. A member was married			42
b. Young adult member left home			43
c. Young adult member began college (or post high school training)			28
d. A member moved back home or a new person moved into the household			42
e. A parent/spouse started school (or training program) after being away from school for a long time			38
IX. Family Legal Violations			
a. A member went to jail or juvenile detention			68
b. A member was picked up by police or arrested			57
c. A member ran away from home			61
d. A member dropped out of school or was suspended from school			38

Family Adaptability, Partnership, Growth, Affection and Resolve (APGAR)

5.1. Now we would ask that you think about the following and check the answer that best describes how you feel most of the time. Please be honest.

a) When something is bothering me, I can ask my family for help.

☐	☐	☐	☐	☐
Never	Hardly	Some of the time	Almost always	Always

b) I like the way my family talks things over and shares problems with me.

☐	☐	☐	☐	☐
Never	Hardly	Some of the time	Almost always	Always

c) I like how my family lets me try new things I want to do.

☐	☐	☐	☐	☐
Never	Hardly	Some of the time	Almost always	Always

d) I like what my family does when I feel mad, happy, or loving.

☐	☐	☐	☐	☐
Never	Hardly	Some of the time	Almost always	Always

e) I like how my family and I share time together.

☐	☐	☐	☐	☐
Never	Hardly	Some of the time	Almost always	Always

Demographic Characteristics

These final few questions ask about your child and his/her family.

8.17. **Is your child:**

☐ Male ☐ Female

8.18. **What is your child's date of birth?**

☐☐ / ☐☐ / ☐☐
DAY MONTH YEAR

8.19. **Who lives with your child currently?**

Person	Their relationship to your child	Their Age	Their sex
1			☐ Male ☐ Female
2			☐ Male ☐ Female
3			☐ Male ☐ Female
4			☐ Male ☐ Female
5			☐ Male ☐ Female
6			☐ Male ☐ Female
7			☐ Male ☐ Female
8			☐ Male ☐ Female

8.20. **Is anyone helping you to complete this questionnaire?**

☐ No ☐ Yes →

If yes, who is helping you:
☐ Your spouse/partner
☐ Your child

→

☐ Other

If other, please specify:

_____

8.21. **Are you:**

☐ Male ☐ Female

8.22. **What is your date of birth?**

☐☐ / ☐☐ / ☐☐
DAY MONTH YEAR

8.23. **Which of the following best describes your current work status?** (check one box only)

☐	☐	☐	☐	☐	☐
Not working due to my child's health	Not working for "other" reasons	Looking for work outside the home	Working full or part-time (either outside the home or at a home-based business	Full time homemaker	Student

8.24. **What is your relationship to this child?** (check one box only)

☐	☐	☐	☐	☐	☐
Biological parent	Step parent	Foster parent	Adoptive parent	Guardian	Other (please explain on the line below)

8.25. **What is the highest grade of school you have completed?**

☐ less than 8 years
☐ 8-12 years
☐ completed high school
☐ completed vocational/technical training
☐ completed college/university
☐ completed graduate school

8.26. **What is your current marital status?** (check one box only)

☐	☐	☐	☐	☐	☐
Married	Widowed	Divorced	Separated	Remarried	Never married

8.27. **Are you currently living with a spouse or partner?**

☐ Yes ☐ No → If no, go to question 8.30.

8.28. **Which of the following best describes your spouse's/partner's current work status?** (check one box only)

☐	☐	☐	☐	☐	☐
Not working due to my child's health	Not working for "other" reasons	Looking for work outside the home	Working full or part-time (either outside the home or at a home-based business	Full time homemaker	Student

8.29 **What is the highest grade of school your spouse/partner has completed?**

- ☐ less than 8 years
- ☐ 8-12 years
- ☐ completed high school
- ☐ completed vocational/technical training
- ☐ completed college/university
- ☐ completed graduate school

The next two questions will allow us to compare your family's health to that of other people in the study who are similar to you.

8.30. **In which category is your total yearly household income before taxes?** (check one box only)

- ☐ Less than $10,000
- ☐ $10,000 - $19,999
- ☐ $20,000 - $29,999
- ☐ $30,000 - $39,999
- ☐ $40,000 - $49,999
- ☐ $50,000 - $59,999
- ☐ $60,000 - $69,999
- ☐ $70,000 - $79,999
- ☐ $80,000 - $89,999
- ☐ $90,000 - $99,999
- ☐ $100,000 or more
- ☐ Don't know

8.31. **Thinking about your total family income, from which sources did your family receive income during the past year?** (check all that apply)

- ☐ Wages and salaries
- ☐ Income from self-employment
- ☐ Family allowance (baby bonus)
- ☐ Unemployment insurance or strike pay
- ☐ Worker's compensation
- ☐ Old Age Security, Guaranteed Income Supplement, Canada or Quebec Pension Plan, Retirement Pension Plan, Super-annuation
- ☐ Dividends and interest on bonds, deposits, and saving certificates
- ☐ Other government sources such as welfare, mother's allowance, etc.
- ☐ Other sources(s), please specify: _____

8.32. **How long ago was your child *first* diagnosed with epilepsy?**

_____ Months ago or _____ Weeks ago

8.33. **Who *first* diagnosed your child with epilepsy?** (check one box only)

- ☐ Family Physician
- ☐ Neurologist
- ☐ Pediatrician
- ☐ Other (please specify) _____

8.34. **Did the doctor who first diagnosed your child with epilepsy prescribe any medications for seizures?**

- ☐ Yes
- ☐ No

8.35. **DATE THIS QUESTIONNAIRE WAS COMPLETED:**

☐☐ / ☐☐ / ☐☐

Neurologists' Questionnaire

Patient's Date of Birth (dd/mm/yy): _____ Site #:_____

Please answer the following questions based on information from this patient's most recent visit and return upon completion

1. Date of patient's last visit (dd/mm/yy): _____ or Date of Telephone F/U (dd/mm/yy)_____
2. Date form completed (dd/mm/yy): _____

If information for 3 thru 7 is unchanged from baseline (diagnosis) visit, please check here and proceed to 8. ☐

3. Seizure type(s): 1) _____ 2)_____
   3)_____ 4)_____
4. Epilepsy syndrome: _____
5. Convulsive status epilepticus:
   ☐ No
   ☐ Yes
6. Exclusive nocturnal seizures:
   ☐ No
   ☐ Yes
7. Age of first seizure (excluding febrile seizure): _____ yrs
8. Does this patient have any family with epilepsy?
   ☐ No
   ☐ Yes
9. Number of AEDs currently: _____
10. Number of AEDs total: _____
11. Is this patient of school age?
    ☐ No

☐ Yes → Grade: ___ ☐ regular class ☐ regular class with resource ☐ special class

12. Does the patient have behavioural problems?
☐ No (normal)
☐ Yes → Please check one: ☐ mild ☐ moderate ☐ severe

Diagnosis: _____

13. Does the patient have cognitive problems?
☐ No (normal)
☐ Yes → Please check one: ☐ borderline ☐ mild ☐ moderate ☐ severe

Diagnosis: _____

14. Does this patient have motor problems?
☐ No
☐ Yes → Please check one: ☐ mild ☐ moderate ☐ severe

Diagnosis: _____

15. Other neurological deficits? Please specify: _____

16. Taking into account all aspects of this patient's epilepsy, how would you rate its severity at his/her last visit? Please check <u>one</u> answer.

☐ Extremely severe
☐ Very severe
☐ Quite severe
☐ Moderately severe
☐ Somewhat severe
☐ A little severe
☐ Not at all severe

17. Rate the following aspects of this patient's epilepsy at his/her last visit.

Check <u>one box</u> using the following 7-point scale:
1 = none or never
7 = extremely frequent, severe or high

	1	2	3	4	5	6	7
Frequency of seizures							
Intensity of seizures							
Falls or injuries during seizures							
Severity of post-ictal period							
Amount of antiepileptic drugs							
Side effects of antiepileptic drugs							
Interference of epilepsy or drugs with daily activities							

Curriculum Vitae

Name: Klajdi Puka

Post-secondary Education and Degrees:

University of Toronto, Mississauga
Mississauga, Ontario, Canada
2009 - 2013 HBSc

Western University
London, Ontario, Canada
2016 - 2021 Ph.D.

Honours and Awards:

Canadian Mental Health Association, Ontario Doctoral Fellowship in Mental Health and Addictions Services Award. 2019.

Canadian Institutes of Health Research - Frederick Banting and Charles Best Canada Graduate Scholarships; 2018 – 2021.

Queen Elizabeth II Graduate Scholarship in Science and Technology (Declined). 2018

First Place, Basic Science Oral Presentation, 31st Annual Paediatric Research Day, Victoria Hospital, London, ON, Canada. 2018

Poster Award, London Health Research Day, Western University, London, ON, Canada. 2018

Ontario Graduate Scholarship. 2017 - 2018

Canadian Society for Epidemiology and Biostatistics Travel Award. 2017

Department of Paediatrics Travel Award, Victoria Hospital, London Health Sciences Center, London, ON, Canada. 2017

Canadian Institutes of Health Research - Canada Graduate Scholarship-Master's. 2016 - 2017

Western Graduate Research Scholarship. 2016 - 2020

Queen Elizabeth II Graduate Scholarship in Science and Technology (Declined). 2016

Related Work Experience:

Biostatistician,
Brain Recovery Project
2020 – Present

Statistical Analyst,
Department of Medicine, Western University
2018 – Present

Methodology and Statistics Consultant,
Department of Epidemiology & Biostatistics, Western University
2017-2018

Research Grants:

Speechley KN, Bax K, Levin SD, Prasad AN, **Puka K**, Secco M, Zou G. *A Community-Based Family Treatment Program for Children with Epilepsy: A Randomized Controlled Trial*. Canadian Institutes of Health Research: $459,000. Co-investigator, 2019 – 2021

Secco M, Speechley KN, **Puka K,** Shah A. *Clinic to Community© Program for Adults with Epilepsy Admitted to Emergency Departments: A Randomized Controlled Trial*. Ontario Brain Institute: $125,000. Co-Principal Investigator, 2019 – 2022

Publications:

Puka K, Bax K, Andrade A …. Speechley KN (2020). A Live-Online Mindfulness-based Intervention for Children Living with Epilepsy and their Families: Protocol for a Randomized Controlled Trial of Making Mindfulness Matter©. Trials 21, 922.

Puka K, Ferro MA, Camfield CS, Levin SD, Smith ML, Wiebe S, Zou G, Speechley (2020). Self-reported quality of life and degree of youth-parent agreement: A long-term follow-up of childhood-onset epilepsy. Epilepsia 61, 2254–2264.

Puka K, Ferro MA, Camfield CS, Levin SD, Smith ML, Wiebe S, Zou G, Anderson KK, Speechley (2020). Long-term quality of life trajectories among individuals diagnosed with epilepsy in childhood. Epilepsia 61, 1453-1463.

Puka K, Speechley KN, Ferro MA (2020). Convulsive status epilepticus in children recently diagnosed with epilepsy and long-term health-related quality of life. Seizure: European Journal of Epilepsy 80, 49-52.

Puka K, Goodwin SW, Ferro MA, Smith ML, Widjaja E, Anderson KK, Speechley KN (2020). Validation of the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55 and QOLCE-16) for use by parents of young adults with childhood-onset epilepsy. Epilepsy & Behavior 104, 106904.

Puka K, Tavares PT, Speechley KN (2019). Social outcomes of adults with childhood-onset epilepsy: a systematic review and meta-analysis. Epilepsy & Behavior 92, 297-305.

Puka K, Ferro MA, Anderson KK, Speechley KN (2019). Prevalence and trajectories of depressive symptoms among mothers of children with newly diagnosed epilepsy: a longitudinal 10-year study. Epilepsia 60, 358-366.

Puka K, Tavares PT, Anderson KK, Ferro MA, Speechley KN (2018). A systematic review of quality of life in parents of children with epilepsy. Epilepsy & Behavior 82, 35-45.

Puka K, Ferro MA, Anderson KK, Speechley KN (2018). Health related quality of life in mothers of children with epilepsy: 10 years after diagnosis. Quality of Life Research, 27, 969-977.

Invited Presentations

Puka K (Dec 2020). Long-term sequelae of childhood-onset epilepsy and epilepsy surgery; Psychiatric and psychosocial outcomes. Neuropsychology Special Interests Group, American Epilepsy Society Annual Meeting, Seattle, WA, USA.

Puka K (Sept 2020). Neuropsychology and epilepsy –what every clinician treating epilepsy should know in 2020. Hot Topics in Epilepsy, North American Epilepsy Congress, Toronto, ON, Canada.

Puka K (Sept 2019). Cognitive outcomes of pediatric epilepsy surgery. Canadian League Against Epilepsy Biennial Conference, Winnipeg, MB, Canada.

Puka K (Jul 2019). Academic achievement and IQ. Functional Impacts of Large Resective or Disconnective Pediatric Epilepsy Surgery: Identifying Gaps and Setting Patient-Centered Outcomes Research Priorities, The Brain Recovery Project, Cleveland, OH, USA.

Puka K (Nov 2018). Development and implementation of a long-term population-based study of children with epilepsy. Seminar Series, Woolcock Institute of Medical Research, Sydney, NSW, Australia.